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THE EFFICACY AND THE SAFETY OF THE INTRAMUSCULAR ADMINISTRATION OF BACITRACIN IN VARIOUS TYPES OF SURGICAL AND CERTAIN MEDICAL INFECTIONS

With an Analysis of 270 Cases

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THE first report on the systemic administration of bacitracin was presented to the American Surgical Association at Quebec in May of 1948 and appeared in October of 1948 in *Annals of Surgery*. The report covered 105 cases of various types of infection, chiefly surgical (5). These patients for the most part received the commercial product manufactured by the company herein referred to as company A, and it was produced by the *surface growth* of the organism.

The number has now reached 270 cases and another report seems to be in order, because we have had further experience with this potent antibiotic produced by a different method, namely by the *deep tank* growth of the organism, manufactured by the company herein referred to as Company B. This experience has covered the period since January of 1948, when temporary specifications were set up by the Food and Drug Administration for the purpose of insuring the efficacy and safety of the antibiotic. The data herewith reported were obtained by means of a co-ordinated study of cases treated by several observers in different parts of the country, planned in such a way as to minimize the personal equation in the appraisal of this drug. The uniformity of the study was insured by the careful preparation and adoption of a summary sheet, which was designed to bring out all of the essential features of the individual cases, particularly with regard to the diagnosis, the duration of the illness, the previous antibacterial agents used to control the infection, the status of the blood, the function of the kidneys before, during, and after treatment, the daily dosage, the interval and the

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total amount of medication used both systemically and locally, the symptoms and signs of infection before, during, and after treatment, the blood levels obtained and the per cent of drug excreted in the urine. Particular stress was laid on the bacteriology before, during, and after treatment with special reference not only to a complete bacteriological analysis of the cases, but whenever possible to the testing of the organisms for susceptibility to bacitracin and other antibiotics. On the basis of these data each observer was asked to give an evaluation of the drug treatment, putting the case into one of four categories. The result was considered to be "excellent," if the response was sudden or dramatic and the infection brought under control within 72 hours; "good," if there was a definite response but somewhat slower in its evolution; "questionable," if the observer felt that the case might have done just as well without the drug as with it; and "no effect," when it was obvious that the infection had gone on its course regardless of the treatment. The observer was also asked to record whether the drug treatment obviated otherwise necessary surgery or permitted less extensive surgery; whether the drug treatment shortened the healing time or failed to do so; and whether the drug treatment permitted primary closure, either immediate or delayed, or an earlier secondary closure. On the summary sheet also there was a graph record of the temperature, in order to correlate the temperature curve with the treatment given. Each case record also had a summary of the history and the course of treatment. These summary sheets with all of the essential data were submitted to the office of the senior author of this paper, where a statistician reviewed each one and asked for further details or corrections, if there were any obvious omissions, inconsistencies or errors. As the records were completed these data were subjected to statistical analysis.

It was felt that such a study was essential in order to obtain as soon as possible a fair and honest judgment regarding the value of this new antibiotic. It was thought that such an appraisal could not be obtained by a more extensive distribution of the drug to large numbers of doctors, who would not have the time or interest to make a detailed record of the history, course, and circumstances of the cases treated. This study is similar to one of the early studies of penicillin made by a somewhat different group and reported by the senior author in *Annals of Surgery* in 1946 (4). We believe that this report has the same authenticity in the literature of surgical infections as the earlier report on penicillin. At the same time, it includes a group of cases of pneumonia treated by Dr. Edward H. Reisner, Jr., at Bellevue Hospital, who was in the original plan but whose cases were not included in the series of surgical infections treated with bacitracin and reported in 1948 (5).

Our combined experience now covers a period of 22 months and the cases may be roughly divided into 3 groups. About 85 patients were treated with the Company A product of bacitracin produced by the surface growth of the organism. About 85 patients were treated with the early product of Company B produced by the deep tank production of the growth of the organism, and about 100 patients were treated by some of the later products of Company B selected particularly for their relatively low toxicity.

Although it had been clearly demonstrated that bacitracin was strikingly effective in the treatment of local infections, both by local injection of an aqueous or saline solution of the drug directly into the area of infection and by local application of the drug to wounds and surfaces either in solution or in ointment form, as reported in March, 1947, and in 1948 (6, 8, 9), the systemic administration of bacitracin had to await the preparation of a somewhat purer product. Well localized infections were cured by the injection of the crude filtrate obtained from the medium in which the organism was grown. The first filtrates were obtained from broth media and later ones from synthetic media. Still later we depended upon concentrated preparations made in our chemistry laboratory by the extraction of the active principle by means of butanol. The earliest commercial product was produced by Company A (surface growth process) in soybean media. At first these preparations contained impurities carried over from this medium and from other by-products

of manufacture. But the manufacturers gradually eliminated many of these impurities and finally gave us a highly soluble, faintly yellowish powder in lyophylized form, which could be dissolved in water or saline and then injected subcutaneously, intramuscularly, or intravenously into animals. These preparations permitted certain pharmacologic studies, which were carried out and reported by Dr. John Scudi and his associates (11, 12, 13). These studies clearly demonstrated that the drug could be well tolerated by laboratory animals in doses which were effective in the control of infection produced experimentally by susceptible organisms, such as the hemolytic streptococcus and the clostridia of gas gangrene. The only evidence of injury to the body tissues (and this was obtained only by large doses) was in the lower nephron of the kidneys of mice. There was no evidence of injury even in these areas in any other animal in the doses which were employed, except slight changes in the kidneys of monkeys. Dogs, rabbits, rats, and cats seemed to be entirely free from even this evidence of toxicity. It was also found that the drug could be tolerated in very much larger doses, if given intramuscularly and subcutaneously than if it were given intraperitoneally or intravenously. Total doses, divided and administered every 4, 6, or 8 hours over a period of one or more days, gave very much less evidence of kidney irritation than if given as a single dose.

On the basis of this experience we began cautiously to administer bacitracin to human beings, first to members of the laboratory staff, and then to patients who were the victims of infection. These patients were studied carefully to demonstrate any evidence of injury to the kidneys or other organs. It was soon demonstrated that albumin appeared in the urine of the majority of these patients on the third, fourth or fifth day of treatment, but that it disappeared with the continuation of treatment. Along with the albumin, but less frequently, granular casts would appear and an increase in the white cells and the epithelial cells. However, these evidences of kidney irritation were always transient and disappeared from the urine either during the course of treatment or as soon as treatment was stopped. In only one case did it interfere with the administration of the drug. During this period, those who were using bacitracin systemically did so with increasing confidence in its safety and freedom from significant toxicity.

At this time Dr. Harry Eagle, finding the spirochetes of syphilis particularly susceptible to bacitracin, began his study of human syphilis with various doses of intramuscularly administered bacitracin. He found that there was remarkable synergistic action between bacitracin and penicillin both in vitro and in vivo in the cure of experimental rabbit syphilis (2). He therefore treated two series of patients, one with bacitracin alone and the other with bacitracin and penicillin together. He observed albumin in the urine of treated cases, but it did not seem to be of clinical significance (1).

After using several lots of the Company A (surface growth process) product with steadily increasing confidence, it was found that with a certain new lot one patient became upset with persistent nausea and vomiting. This occurred at a time when the Company A laboratories were trying to step up their production, and it was thought that something had crept into the manufacture, carrying with it some toxic factor. No further patients were treated with this lot and with subsequent lots these toxic manifestations were absent. We became bold enough, thereafter, to increase the dosage gradually to 30,000 to 50,000 units every 6 hours in order to have a wider therapeutic margin.

A patient with malignant endocarditis, which had not come under control with 20 million units of penicillin or 8 grams of streptomycin a day, was given 50,000 units of bacitracin every 6 hours and later the same dose every 4 hours without evidence of toxicity. There was improvement, but our supply of bacitracin became exhausted and treatment was stopped. The patient then became much worse and several days later when more bacitracin became available, he was moribund. He was given 100,000 units every 4 hours, but it did not save him. At autopsy there was some evidence of tubular injury, possibly due in part to bacitracin, but Professor H. P. Smith of the Department of Pathology gave his opinion that no pathological changes were found which could not be accounted for by the disease itself.

In the meanwhile 13 other pharmaceutical houses undertook the preparation of bacitracin

and all ran into difficulties. Some of these firms were determined to find a way to produce the antibiotic by deep growth in large tanks. Company B was in the van in this race, but ran into a number of difficulties before solving the problem of deep tank production. When the Company A laboratories realized that if a deep tank method were found, surface growth could not compete with it economically, they arranged with the Company B to turn over to them all of their experience and their whole stock of bacitracin and agreed to discontinue production. Thereafter the only material made by the surface growth process was distributed to the study units under the Company B label, although the original Company A lot numbers were retained.

The units which had been set up early in the program had on their hands a stock of the Company A material, which they continued to use on their patients. These included the units in Presbyterian Hospital, New York, in Bellevue Hospital, New York, in Charity Hospital in New Orleans, and in the Cincinnati General Hospital. Using the Company A product, these units generally started with 20,000 units every 6 hours for an adult. If there was no response in 24 to 48 hours, the dose was not infrequently increased to 30,000, 40,000, or 50,000 units. Therefore, when the deep tank product became available, the same doses were employed.

The two new units set up in the University Hospital at the University of Pennsylvania in Philadelphia and in the Brooke General Hospital at Fort Sam Houston had little experience with the Company A product and their first clinical trials were carried out with the early deep tank product of Company B. In the Brooke General Hospital the daily doses were generally limited to 80,000 units. Over a period of 6 months about 20 patients were treated. About half of the patients received 10,000 units and the other half, 20,000 units every 6 hours. In the Philadelphia unit their first experience was with cases of endocarditis, which had failed to respond to penicillin and therefore it seemed wise to give as large a dose as could be tolerated. Most of their patients therefore received 50,000 units every 6 hours for a total of 200,000 units daily.

It was soon evident that the reports from these two units were disturbing, because not only did albumin appear in the urine 2 to 3 days after bacitracin treatment was started, but there was frequently a shower of cellular elements from the kidney. Furthermore, the patients developed a lethargy which persisted for some time and along with it a rise in the retained nitrogen, as indicated either by the tests for the serum urea nitrogen or nonprotein nitrogen. At the same time there was frequently a fall in the filtration rate of phenolsulfonphthalein and a lowering of specific gravity. Such findings could not always be correlated with the dosage. The difference often seemed to be due to individual idiosyncrasy rather than to the amount of the material administered.

A month or so later the other units gradually used up their supply of Company A material and began to treat patients with the early product of Company B. One by one all of the units found that they were running into similar difficulties, which they had not experienced with the Company A material.

With his knowledge of renal physiology as a background, a study was carried out at the University Hospital in Philadelphia by Dr. Alexander Michie, to determine the effect on renal function of the big doses used by the Philadelphia unit. Figures were obtained in the cases of 6 patients treated with two different lots of the early Company B product in doses of 50,000 units every 6 hours for a period of from 3 to 15 days. It was found that there was an appreciable diminution of glomerular and tubular filtration as well as renal blood flow. These results were not uniform. There was wide variation in different individuals, but there was a definite average decrease in all of these functions. At the same time albumin and an increase in the cellular elements appeared in the urine (7).

These clinical and laboratory experiences made it obvious that it would be necessary to study the problem of toxicity with renewed zeal. All of the records were therefore gathered together and the case histories were studied from the point of view of the lot numbers used and the dosage. These data were correlated with the laboratory and clinical

evidence of kidney irritation. The results of this study are shown in Tables I and II.

At the same time a series of experiments were carried out in the laboratory in order to compare the Company A material produced by surface growth with the product of Company B grown in the deep tanks. Six lots from each firm, which had been used clinically, were selected and saline solutions of the antibiotic were injected subcutaneously into mice in doses ranging from 250 to 1,000 units. Four hundred and eighty-four mice were used in this study. With each lot the death rate was noted and after a period of several days the surviving mice were subjected to autopsy and notes were made with regard to the evidence of gross renal pathology.

When all of the clinical and laboratory data were gathered together, it was obvious that the early product of Company B was definitely more toxic than the Company A material. Furthermore, these data indicated that different lots of Company B material varied considerably from one another in their toxicity. This variation between different lots was confirmed by the results of the toxicity tests carried out in the laboratory of Dr. Henry Welch of the Food and Drug Administration.

No LD50 tests were carried out by the Food and Drug Administration with the Company A surface growth product, because specifications were not set up until January of 1948, after Company A had ceased its production and had turned over all of its supply to Company B. At that time it was felt that an LD50 of 200 units for a 20 gram mouse would provide an adequate margin of safety. The early product made by the deep tank method met this specification, but the Food and Drug Administration tests revealed that different lots varied all the way from 224 to 500 units, while the assay of potency per milligram of material remained fairly constant (see Table II). Furthermore, it was found that the Food and Drug Administration tests could be correlated with the laboratory and clinical data mentioned above. It was then clear that Major Pulaski, Dr. Zintel, and Dr. Michie had been making their observations for the most part with relatively toxic lots, while Dr. Longacre and Dr. Reisner had been working with lots of low toxicity.

TABLE I.—DEGREE OF TOXICITY ACCORDING TO LOT NUMBERS USED IN THE INTRAMUSCULAR ADMINISTRATION OF BACITRACIN PREPARED BY THE SURFACE GROWTH METHOD

Lot Number	Number of cases*	Daily dosage	Some evidence of kidney damage before Rx	Toxicity with treatment		
				None or slight transient†	Moderate transient‡	Disturbing§
August, 1946 to March, 1948:						
Co. A 100	3	12–300,000	2	3	0	0
Co. A 110	2	60–600,000	1	1	1	0
Co. A 113	8	30– 80,000	4	4	4	0
Co. A 114	8	60–120,000	6	5	3	0
Co. A 115	6	40–120,000	4	3	3	0
Co. A 116	1	80,000	1	0	0	1
Co. A 116S	2	67–120,000	0	1	1	0
Co. A 130	5	48–100,000	3	2	3	0
Co. A 131	3	40– 90,000	1	2	1	0
Co. A 140	6	10–160,000	2	3	3	0
Co. A 141	14	40–125,000	1	11	3	0
Co. A 142	26	30–240,000	7	14	12	0
Co. A 143	13	22–264,000	8	5	8	0
Co. A 144	11	47–132,000	6	2	9	0
Co. A 145	6	40–196,000	3	2	4	0

*A few cases were treated with more than one lot and are included with each lot used.
†Albumin 0 or 1 plus, 0 or occasional granular cast, a few white cells and epithelial cells.
‡Albumin 2–3 plus or albumin 4 plus one day only, few to moderate granular casts, white cells, epithelial cells, rare red cells. Treatment not interrupted.
§Albumin 4 plus, moderate to many granular casts, white cells, epithelial cells and few to moderate red cells, or nausea and vomiting or significant rise in retained nitrogen, or considered advisable to stop treatment for any other reason.

It was then agreed that further systemic use of the antibiotic by all of the units should be limited to material which could meet the specification of LD50 of 500 for a 20 gram mouse. Company B had demonstrated that it could meet this specification. It was further agreed that for the time being the initial dose should be approximately 200 units per kilogram of body weight. This dose might be doubled or tripled if occasion warranted it in the judgment of the observer. This plan has been followed since July of 1948, and the favorable results in the last hundred cases have amply justified this program.

TABLE II.—DEGREE OF TOXICITY ACCORDING TO LOT NUMBERS USED IN THE INTRAMUSCULAR ADMINISTRATION OF BACITRACIN PREPARED BY THE DEEP TANK METHOD

Lot Number	F.D.A. LD 50 20 gm. mouse	Number of cases‖	Daily dosage	Some evidence of kidney damage before Rx	Toxicity with treatment		
					None or slight transient*	Moderate transient†	Disturbing‡
January, 1948 to June, 1948:							
Co. B 471212S	287± 18	20	40–260,000	10	2	8	10
Co. B 471217S	255± 20	5	88–260,000	3	0	4	1
Co. B 471231S	240± 21	8	40–280,000	3	1	5	2
Co. B 480114S	283± 18	19	40–392,000	8	6	10	3
Co. B 480120S	361± 23	22	14–400,000	9	11	8	3
Co. B 480210S	262± 17.7	14	16–160,000	3	5	3	6
Co. B 480212S	224± 15.2	10	42–200,000	10	1	4	5
Co. B 480218S	500 or less	13	40–200,000	6	6	6	1
July, 1948 to June 1, 1949:							
Co. B 480408	500	13	20– 80,000	8	8	5	0
Co. B 480420	<500	42	2–120,000	16	22	19	1
Co. B 480512	322± 26.8	4	40– 80,000	0	0	1	3
Co. B 480520	435± 80.9	2	10– 40,000	0	0	1	1
Co. B 480616	about 500	37	2–180,000	12	26	10	1¶
Co. B 480623	>500	13	2– 80,000	9	9	3	1**

‖A few cases were treated with more than one lot and are included with each lot used.
¶Patient in extremis when bacitracin was started.
**Bacitracin was given every 4 hours by mistake.
*Albumin 0 or 1 plus, 0 or occasional granular cast, a few white cells and epithelial cells.
†Albumin 2–3 plus or albumin 4 plus 1 day only, few to moderate granular casts, white cells, epithelial cells, rare red cells. Treatment not interrupted.
‡Albumin 4 plus, moderate to many granular casts, white cells, epithelial cells and few to moderate red cells, or nausea and vomiting or significant rise in retained nitrogen, or considered advisable to stop treatment for any other reason.

In order to be certain that the low incidence of nephrotoxic responses in the patients receiving the bacitracin with the LD50 of 500 was not simply a question of low dosage, 6 patients during this period were given material from two lots which fell short of this specification. Table II reveals that 3 of 4 patients receiving lot No. 480512 in the same dosage gave disturbing symptoms and signs of toxicity. One of these (Case 5) had received the Company A material the year before for over a month in a daily dose 50 per cent larger without evidence of toxicity. The toxic symptoms and signs all disappeared in the others when the treatment was changed to the lots meeting the specification. Virtually the same results were obtained in the 2 patients treated with lot No. 480520. These observations with regard to dosage are amply confirmed by the fact that the toxic effects observed by Major Pulaski were all obtained with doses of the antibiotic not exceeding 80,000 units per day with lots of relatively high toxicity.

This rather long dissertation on the problem of toxicity seems necessary in order to help the reader of this report to understand the difficulties which have been met and largely overcome during the course of this study. The first phase was a period of calm, the second a storm of uncertainty, and the third phase a period of increasing confidence in the efficacy and safety of this new antibiotic.

Further efforts are being made to reduce the toxic factor still more or to eliminate it entirely from the active principle. If by the present methods of production the manufacturers can meet this specification of LD50/500 we believe that bacitracin should be made available for more extended use in hospitals. Only those patients should be treated who can be watched carefully and in whom urinalyses can be performed daily and tests for retained

nitrogen made once or twice a week. The first clinical sign of toxicity is lack of appetite and if this increases, nausea may occur and in still more toxic cases, vomiting. The more subtle changes can be determined by the microscopic examination of the urine and the test for the nonprotein nitrogen retained in the blood. If any patient needs bacitracin treatment, an albuminuria of 1 plus to 3 plus or an increase of 50 to 100 per cent in the non protein nitrogen do not constitute a contraindication to continued use of the drug, and it should not be stopped unless the symptoms become really alarming, because the toxic factor is far outweighed by the therapeutic value of bacitracin and one can be sure that these changes are reversible and that the kidney function will be restored to normal sooner or later after cessation of treatment. This fact was repeatedly demonstrated in every case which was brought back for checkup. Many patients with infection show some evidence of kidney irritation before bacitracin is started, either albumin in the urine, casts, an increased number of cells, or a high nonprotein nitrogen. This is not a contraindication to the use of bacitracin, because an analysis of our data shows no correlation between toxic manifestations and previous evidence of kidney damage. These signs do not usually increase during treatment, a fact suggesting that the toxic reaction is more a question of individual idiosyncrasy rather than the result of damage already present in the kidney.

ANALYSIS OF RESULTS

Completed summary sheets for 270 cases from the different units have been turned in to the central office. These include 25 cases of pneumonia which Dr. Reisner has carefully studied and has reported (10). Suffice it to say here that his experience clearly indicates that bacitracin is effective in curing pneumococcus pneumonia, that most of the organisms producing this disease are susceptible to bacitracin, and that the clinical symptoms disappear promptly following its use. Favorable results have been obtained by doses as low as 10,000 or 15,000 units every 6 hours, but doses of 30,000 units every 6 to 8 hours for a period of 5 to 7 days are advocated in cases with pneumococcus bacteriemia. Reisner recommends the determination of the sensitivity of the invading organism and giving doses large enough to produce blood levels ten times this sensitivity. In some of his cases he gave as high as 99,000 units every 6 hours, and with the lots which he employed, the evidence of nephrotoxicity was minimal. He considers that bacitracin is only slightly more toxic than streptomycin (3). None of his patients showed any permanent or serious damage to the kidneys. He recommends the use of bacitracin in cases of pneumonia where there is a sensitive organism which does not respond to penicillin. He found a high level of bacitracin in the pleural exudate and recommends its intrapleural local instillation in cases in which organisms are present in the pleural fluid.

Of the remaining cases, 7 patients have received the drug prophylactically. In none of these did infection develop, but little can be said of its prophylactic use at this time. The other 238 cases represent 76 different clinical groups. They are listed in Table IIIa and the results obtained are shown in adjacent columns. Forty-five of these are called miscellaneous because there was only 1 case in each diagnostic classification. Thirty-two had 2 cases under each of 16 different diagnoses. All the other clinical entities had 3 or more, the largest group being classified as cellulitis, which is a diffuse inflammation of the skin and subcutaneous tissues with very little evidence of localization of the process in the early stages of the lesion.

If we consider the "excellent" and "good" results as favorable and the "questionable" and "no effect" as unfavorable, we find that in this whole group about two-thirds gave a favorable response to bacitracin. There are about twice as many cases in the "good" category as in the "excellent."

Certain of the groups are worthy of special note. For example, it is seen that in the cases of cellulitis, there are more excellent responses than good. This is also true of synergistic gangrene and staphylococcal meningitis. Furthermore, in infected accidental wounds and in carbuncles there was a better than average percentage of favorable results. Particularly poor results were obtained in endocarditis, all

TABLE IIIa.—OVERALL RESULTS OF INTRAMUSCULAR BACITRACIN TREATMENT IN 270 CASES ACCORDING TO DIAGNOSIS

Diagnosis	Total cases	Results of treatment			
		Excellent	Good	Questionable	No effect
Cellulitis	31	16	10	2	3
Pneumonia	27	16	2	0	9
Infected accidental wound	20	6	12	1	1
Deep abscess	19	5	10	2	2
Infected operation wound	*14	2	5	2	5
Chronic osteomyelitis	12	0	4	4	4
Carbuncle(s)	8	1	6	0	1
Endocarditis	8	0	0	1	7
Prophylactic	7	1	6	0	0
Ulcer(s) of leg(s)	7	0	4	2	1
Undermining burrowing ulcer	6	2	2	0	2
Staphylococcic meningitis	4	4	0	0	0
Synergistic gangrene	5	4	1	0	0
Acute osteomyelitis	4	0	3	0	1
Superficial abscess	4	0	2	1	1
Multiple furuncles	4	0	1	1	2
Ulcerative colitis	4	0	0	2	2
Human bite infection	3	2	0	0	1
Furuncle	3	0	3	0	0
Actinomycosis	3	0	1	2	0
Miscellaneous (2 each)†	32	5	13	3	11
Miscellaneous (1 each)*	45	6	22	9	8
Totals	270	70	107	32	61

Favorable results in 65.6 per cent of cases

†Both favorable: Staphylococcus septicemia, infected compound fracture, infectious eczematoid dermatitis, recurrent erysipelas, epidural abscess, sinus of back, acute mediastinitis.

One favorable, one unfavorable: pyelonephritis, regional ileitis, brain abscess, bronchiectasis.

Both unfavorable: thrombophlebitis, peritoneal abscess, multiple liver abscesses, ulcers of perineum, pemphigus.

*Favorable: septic abortion, gangrenous ulcer of back, sacrococcygeal abscess, infected mosquito bite, chronic vaginitis, chronic bronchitis, suppurative arthritis, pansinusitis, superficial sinus of thigh, infected tumor, subdural abscess, ulcer of groin, cervical adenitis, calcified abscess, decubitus ulcer, tuberculosis of glands of neck, felon left thumb, gangrene (symbiotic), paronychia, infected sebaceous cyst, ulcer of vulva and foreskin, ulcer of gluteal fold, chronic paranasal sinusitis, edema of face and neck, choroiditis, cystitis, chronic osteomyelitis of bones of face with pansinusitis. Septic (mixed) meningitis.

Unfavorable: ulcers of perineum, wrist and neck; cholangiitis, influenza meningitis, gangrene of foot, peritonitis, chronic bronchopneumonia, strangulated hernia, Harada's disease, gas gangrene, ulcer of arm, gangrene of foot with tetanus, basal skull fracture, sinus of chest wall, meningitis, panophthalmitis, Hodgkin's disease, tetanus.

of which were unfavorable. This is probably a reflection of the present limitation of dosage. The wide variety of diagnoses makes it clearly apparent that an opportunity has been given to bacitracin to try its strength against all

TABLE IIIb.—RESULTS OF TREATMENT WITH INTRAMUSCULAR BACITRACIN ONLY

Diagnosis	Total cases	Results of treatment			
		Excellent	Good	Questionable	No effect
Pneumonia	27	16	2	0	9
Cellulitis	18	11	3	2	2
Deep abscess	11	3	6	1	1
Infected accidental wound	10	3	6	1	0
Endocarditis	7	0	0	1	6
Chronic osteomyelitis	5	0	0	3	2
Infected operation wound	5	0	0	1	4
Human bite infection	3	2	0	0	1
Prophylactic	3	0	3	0	0
Recurrent erysipelas	2	1	1	0	0
Furuncle	2	0	2	0	0
Superficial abscess	2	0	2	0	0
Pyelonephritis	2	0	1	1	0
Ulcer of leg	2	0	1	1	0
Carbuncle(s)	2	0	1	0	1
Acute osteomyelitis	2	0	1	0	1
Thrombophlebitis	2	0	0	2	0
Peritoneal abscess	2	0	0	0	2
Undermining burrowing ulcer	2	0	0	0	2
Miscellaneous (1 each)	24	3	7	6	8
Totals	133	39	36	19	39

Favorable results in 56.4 per cent of cases

kinds and conditions of infections, including those in which the organism is not known or cannot be determined. It has also been tried in many cases which are probably not infections at all and which have been included in the "no effect" column. Furthermore, no patient was refused treatment when the call was made for bacitracin. Even though he was moribund, it was given to the patient in the hope that it might turn the tide. Some of the patients with infections thought to be hopeless nevertheless surprised everyone and recovered.

Tables IIIb and IIIc show that about one half of the patients were treated solely with systemic bacitracin, while the other half received the drug both locally and systemically. The results in the latter (75.6 per cent) seem to be much better than in the former (56.4 per cent), but it is obvious that these two

TABLE IIIC.—RESULTS OF TREATMENT WITH INTRAMUSCULAR AND LOCAL BACITRACIN

Diagnosis	Total cases	Results of treatment			
		Excellent	Good	Questionable	No effect
Cellulitis	11	4	7	0	0
Infected accidental wound	9	2	6	0	1
Infected operation wound	9	2	5	1	1
Deep abscess	8	2	4	1	1
Chronic osteomyelitis	6	0	4	1	1
Staphylococcus meningitis	4	4	0	0	0
Synergistic gangrene	5	4	1	0	0
Carbuncle(s)	5	1	4	0	0
Ulcer(s) of leg	5	0	3	1	1
Undermining burrowing ulcer	4	2	2	0	0
Prophylactic	4	1	3	0	0
Actinomycosis	3	0	1	2	0
Multiple furuncles	3	0	1	0	2
Infected compound fracture	2	1	1	0	0
Infectious eczematoid dermatitis	2	1	1	0	0
Epidural abscess	2	0	2	0	0
Acute osteomyelitis	2	0	2	0	0
Mediastinitis	2	0	2	0	0
Sinus of back	2	0	2	0	0
Regional ileitis	2	0	1	0	1
Brain abscess	2	0	1	0	1
Superficial abscess	2	0	0	1	1
Ulcers of perineum	2	0	0	0	2
Ulcerative colitis	2	0	0	0	2
Miscellaneous (1 each)	33	5	17	4	7
Totals	131	29	70	11	21
	Favorable results in 75.6 per cent of cases				
Use of local bacitracin Uncertain	6	2	1	2	1

TABLE IV.—RESULTS OF INTRAMUSCULAR TREATMENT WITH BACITRACIN AFTER FAILURE WITH OTHER FORMS OF SYSTEMIC TREATMENT

Systemic treatment	Total cases	Results of bacitracin treatment			
		Excellent	Good	Questionable	No effect
Penicillin only	37	7	14	5	11
Penicillin and streptomycin	13	0	5	2	6
Penicillin and sulfonamide	31	7	11	4	9
Penicillin and aureomycin	2	0	2	0	0
Penicillin and other	1	0	1	0	0
Penicillin, streptomycin and sulfonamide	28	9	7	3	9
Penicillin, aureomycin and sulfonamide	1	0	1	0	0
Penicillin, sulfonamide and other	5	0	3	0	2
Penicillin, streptomycin, sulfonamide and aureomycin	2	1	1	0	0
Penicillin, streptomycin, sulfonamide and other	5	0	1	2	2
Penicillin, aureomycin, sulfonamide and other	1	0	0	0	1
Sulfonamide only	7	2	3	2	0
Sulfonamide and streptomycin	1	0	0	1	0
Sulfonamide and other	1	0	0	0	1
Sulfonamide, streptomycin and other	1	0	0	1	0
Aureomycin only	1	0	0	1	0
Other systemic treatment	3	1	2	0	0
Other systemic treatment unknown	11	3	3	4	1
Totals	151	30	54	25	42
	Favorable results in 55.6 per cent of cases				
No other previous systemic treatment	119	40	53	7	19
	Favorable results in 78.1 per cent of cases				

series are not comparable because in the former group the infections were more serious, the inflammation was more diffuse and often was not sufficiently localized to permit local treatment. Many of the latter group had the benefit of surgical drainage and the removal of dead tissue or slough and the drug could be applied to the area of infection in a concentration far above that which could be reached by systemic injection alone. Nevertheless, the favorable response in cases of cellulitis, synergistic gangrene, and acute osteomyelitis clearly demonstrates the value of a drug coming through the blood stream to the area of infection and limiting its spread by infiltration into the periphery of the lesion. A study of these two subsidiary tables clearly reveals, however, that many of the patients treated with systemic bacitracin alone could have had the advantage of combined local treatment, and the figures suggest that the results for this group might have been improved thereby.

TABLE V.—RESULTS OF SYSTEMIC TREATMENT WITH BACITRACIN ACCORDING TO THE DURATION OF ILLNESS BEFORE THE INITIATION OF BACITRACIN TREATMENT

Duration of symptoms	Total cases	Results of bacitracin treatment			
		Excellent	Good	Questionable	No effect
Previous systemic treatment					
1 day	4	2	2	0	0
2 days	4	2	1	1	0
3 days	6	2	2	1	1
4 to 7 days	18	5	5	4	4
8 to 15 days	23	5	12	1	5
16 to 30 days	24	6	7	4	7
1 to 6 months	22	3	7	3	9
7 to 12 months	8	0	0	3	5
1 to 5 years	25	2	12	3	8
Over 5 years	5	0	3	0	2
Totals	139	27	51	20	41
No previous systemic treatment					
1 day	10	5	5	0	0
2 days	13	5	7	1	0
3 days	8	3	4	0	1
4 to 7 days	27	7	11	5	4
8 to 15 days	13	1	11	1	0
16 to 30 days	4	1	2	0	1
1 to 6 months	5	1	2	0	2
7 to 12 months	1	0	0	0	1
1 to 5 years	4	0	3	0	1
Over 5 years	1	0	1	0	0
Totals	86	23	46	7	10
Pneumonia cases omitted	27	16	2	0	9
Previous treatment unknown	11	3	3	4	1

About three-fifths of the 270 patients had had previous treatment and were sent for bacitracin treatment because these methods had failed. The authors recognize fully that the percentage (56 per cent) of these failures is far higher than for all patients with infections coming to a doctor's office or to an outpatient clinic. These were all seriously ill patients requiring hospitalization and many of them had been ill for a long time. The units set up for the appraisal of bacitracin were known to have a new method of treatment available. Therefore patients not responding to other forms of treatment naturally gravitated toward these centers or were referred there by their local doctors. They had been given the best treatment that their doctors knew how to give for their particular trouble and yet they had failed to respond to the initial treatment or to a combination of treatments. Nevertheless there was a favorable response to bacitracin in 55.6 per cent. This breakdown of the cases is shown in Table IV. The great majority of these patients would almost certainly have gone on with their infection to prolonged, temporary, or permanent disability or death. Therefore it seems fair to call these "salvaged cases" for whose recovery bacitracin should be given full credit. With regard to previous treatment, 126 had received either penicillin alone or penicillin in combination with other drugs. The three largest groups were: "penicillin only," in which there were 37; "penicillin and some sulfonamide," 31; "penicillin, streptomycin and some sulfonamide," 28. Of the 96 cases in these three main categories of previous penicillin treatment, there were 23 which gave a brilliant response to bacitracin, and in 32 it was called "good," a total favorable response of 57 per cent.

Of the 119 cases that had had no previous systemic treatment the favorable results were 78.1 per cent. This difference can be explained largely on the basis of earlier treatment in the latter group.

This would seem to indicate that if the primary treatment had been bacitracin, the results in the first group would have been better. It is obvious that the cases of patients who had had previous treatment were of longer standing than of those who had none. The infection had gained a deeper foothold and the organisms were often resistant to penicillin and the other antibacterial agents which had been employed. Thus the chances of success with bacitracin in the first group were greatly prejudiced. When these cases are studied from the point of view of the duration of the illness before treatment, it is seen in Table V that in the patients who had failed to respond to previous treatments, almost one-half of them (43 per cent) had chronic infections,

TABLE VIa.—RESULTS OF BACITRACIN THERAPY ACCORDING TO THE BACTERIA CULTURED FROM THE LESIONS

Bacteriology	Total cases	Results of treatment			
		Excellent	Good	Questionable	No effect
Hemolytic streptococcus, pure	4	0	2	0	2
Hemolytic streptococcus, mixed	45	11	21	5	8
Nonhemolytic streptococcus, pure	3	0	2	0	1
Nonhemolytic streptococcus, mixed	30	5	9	5	11
Coagulase positive staphylococcus, pure	31	7	19	0	5
Coagulase positive staphylococcus, mixed	40	8	22	3	7
Coagulase negative staphylococcus, pure	4	1	2	0	1
Coagulase negative staphylococcus, mixed	20	3	12	0	5
Coagulase unknown staphylococcus, pure	34	10	13	7	4
Coagulase unknown staphylococcus, mixed	28	10	7	4	7
Other aerobic cocci, pure	3	1	0	0	2
Other aerobic cocci, mixed	7	2	1	0	4
Gram positive aerobic bacilli, pure	0	0	0	0	0
Gram positive aerobic bacilli, mixed	35	8	11	3	13
Culture not taken	43	13	11	10	9

TABLE VIb.—RESULTS OF BACITRACIN THERAPY ACCORDING TO THE BACTERIA CULTURED FROM THE LESIONS

Bacteriology	Total cases	Results of treatment			
		Excellent	Good	Questionable	No effect
Escherichia coli, pure	3	0	1	0	2
Escherichia coli, mixed	19	2	11	4	2
Proteus, pure	1	0	1	0	0
Proteus, mixed	19	2	8	2	7
Other gram negative aerobic bacteria, pure	5	1	1	2	1
Other gram negative aerobic bacteria, mixed	25	6	11	3	5
Anaerobic and microaerophilic cocci, pure	0	0	0	0	0
Anaerobic and microaerophilic cocci, mixed	22	4	10	0	8
Clostridia, pure	0	0	0	0	0
Clostridia, mixed	10	0	4	3	3
Gram positive anaerobic bacteria, pure	0	0	0	0	0
Gram positive anaerobic bacteria, mixed	2	2	0	0	0
Gram negative anaerobic bacteria, pure	0	0	0	0	0
Gram negative anaerobic bacteria, mixed	6	1	0	2	3

that is, their symptoms had lasted for over a month, whereas in the "no previous treatment" group the percentage of chronic cases was only 13 per cent. Thus by the time the first group received treatment, the organisms had not only become more firmly entrenched, but there were unquestionably factors of malnutrition and anemia with necrosis of tissue, all of which interfered with a successful outcome. In both of these groups the table clearly indicates that in general the earlier that treatment was administered, the better were the results obtained. All of those in both groups with symptoms lasting for only 24 hours responded favorably, but unfavorable responses began to appear as the duration of illness increased. In patients with symptoms lasting for 7 days or less in whom previous treatment had failed, bacitracin was successful in 66 per cent. In the cases of 7 days' duration or less with no previous treatment, the favorable response to bacitracin was 81 per cent. Nevertheless, it is seen that in 5 patients with chronic conditions that had been going on for over a month and which had failed to respond to other agents, the responses to the treatment with bacitracin were brilliant.

In the majority of cases a careful and complete bacteriological analysis of the purulent exudate was made, but in a certain number this was impossible. The largest group of those in which no culture was taken were cases of cellulitis, usually caused either by the hemolytic streptococcus or the Staphylococcus aureus. It is always difficult to obtain a culture, if there is no breakdown of tissue. Where there was an exudate, however, analysis was made and all of the organisms which were recovered were subjected to tests for susceptibility to bacitracin and penicillin and in many instances to streptomycin as well (see Tables VIa and b).

TABLE VIIa.—SUSCEPTIBILITY AND RESISTANCE TO BACITRACIN AND PENICILLIN OF CERTAIN OF THE BACTERIA CULTURED FROM THE LESIONS

Bacteriology	Bacitracin S. Penicillin S.	Bacitracin S. Penicillin R.	Bacitracin R. Penicillin S.	Bacitracin R. Penicillin R.
Hemolytic streptococcus	22	13	1	3
Nonhemolytic streptococcus	12	12	0	3
Coagulase positive staphylococcus	26	34	2	3
Coagulase negative staphylococcus	11	8	1	1
Coagulase unknown staphylococcus	19	18	6	0
Other aerobic cocci	4	3	0	2
Anaerobic cocci	15	3	0	4
Gram negative bacilli	0	4	0	66
Gram positive bacilli	7	6	1	9
Clostridia	6	3	0	1
Totals	122	104	11	92

S.—Susceptible; R.—Resistant

Very often a bacteriological laboratory will report the *predominant* organism in a given culture rather than give a complete list of all species present. Many laboratories make no anaerobic cultures. Thus many *significant* organisms are missed. In this series an effort was made to find all of the representative organisms and in doing so it was found that the majority of cases were infected with a mixture of organisms. This is particularly true of chronic cases. Only 88 of the 238 cases had organisms in pure culture, and unless the 43 cases from which no cultures were taken were in fact pure infections, which is unlikely, the remainder had mixed cultures, which totaled 107. The results clearly indicate that even with mixed cultures bacitracin is effective in controlling the infection. This is due to the fact that bacitracin has a very wide antibacterial spectrum and is not inhibited as is penicillin by the penicillinase producers, which are so frequently present in mixed infections. These include not only a large number of species of aerobic gram negative rods, but even among the staphylococci which are resistant, we find many which produce penicillinase. It is of interest to note that the coagulase positive staphylococci are the only ones in which pure cultures approach closely in number the mixed cultures. Probably the strains of staphylococci for which the coagulase test was not done were for the most part pathogenic.

The low incidence of the hemolytic streptococci is a reflection of the secondary role which they play since the advent of the sulfonamides. It is not surprising that the aerobic gram negative rods are seldom present in pure cultures, as they are essentially saprophytes, but that this was true of the anaerobic and microaerophilic cocci was somewhat unexpected.

Of particular interest is a comparison of the cultures in their susceptibility to bacitracin and penicillin. Table VIIa shows that 122 species were susceptible to both; 104 were susceptible to bacitracin and resistant to penicillin, while only 11 were resistant to bacitracin and susceptible to penicillin. Thus it is seen that when there was a difference in susceptibility to these two antibiotics, the ratio was about 10 to 1 in favor of bacitracin. This ratio is twice as great in favor of bacitracin as appeared in a similar study 2 years ago (6). This would seem to indicate that as time goes on an increasing number of organisms are found to be resistant to penicillin and still are susceptible to bacitracin. Again it must be remembered that this is not the ratio one would meet with in cultures from a doctor's office practice or an ordinary clinic. It applies solely to this series, which contains a majority of cases which had failed to respond to previous treatment. In this series 92 strains were resistant to both bacitracin and penicillin, the great majority of these being aerobic gram negative bacilli. It is seen that the balance in favor of bacitracin is most striking with the coagulase positive staphylococci and the streptococci, both hemolytic and nonhemolytic, but it is true of every bacterial group. It must be remembered, of course, that a large portion of these patients had had penicillin. It is not known whether the organisms were originally susceptible and developed a resistance to penicillin or were originally resistant.

If this table showing bacterial susceptibility to bacitracin and penicillin is broken down so as to reveal the difference between the group

TABLE VIIb.—SUSCEPTIBILITY AND RESISTANCE TO BACITRACIN AND PENICILLIN OF CERTAIN OF THE BACTERIA CULTURED FROM THE LESIONS OF PATIENTS WITH PREVIOUS PENICILLIN TREATMENT

Bacteriology	Bacitracin S. Penicillin S.	Bacitracin S. Penicillin R.	Bacitracin R. Penicillin S.	Bacitracin R. Penicillin R.
Hemolytic streptococcus	13	9	0	3
Nonhemolytic streptococcus	6	9	0	1
Coagulase positive staphylococcus	12	27	0	2
Coagulase negative staphylococcus	6	3	1	1
Coagulase unknown staphylococcus	1	13	1	0
Other aerobic cocci	3	2	0	1
Anaerobic cocci	8	3	0	3
Gram negative bacilli	0	2	0	52
Gram positive bacilli	2	3	0	5
Clostridia	3	0	0	0
Totals	54	71	2	68

S.—Susceptible, R.—Resistant
Note—Cases in which previous treatment is unknown are not included.

TABLE VIIc.—SUSCEPTIBILITY AND RESISTANCE TO BACITRACIN AND PENICILLIN OF CERTAIN OF THE BACTERIA CULTURED FROM THE LESIONS OF PATIENTS WITH NO PREVIOUS PENICILLIN TREATMENT

Bacteriology	Bacitracin S. Penicillin S.	Bacitracin S. Penicillin R.	Bacitracin R. Penicillin S.	Bacitracin R. Penicillin R.
Hemolytic streptococcus	9	4	1	0
Nonhemolytic streptococcus	4	3	0	1
Coagulase positive staphylococcus	13	7	2	1
Coagulase negative staphylococcus	4	4	0	0
Coagulase unknown staphylococcus	12	5	5	0
Other aerobic cocci	1	1	0	1
Anaerobic cocci	6	0	0	1
Gram negative bacilli	0	2	0	11
Gram positive bacilli	3	2	0	4
Clostridia	3	2	0	1
Totals	55	30	8	20

S.—Susceptible, R.—Resistant
Note—Cases in which previous treatment is unknown are not included.

which had been previously treated with systemic penicillin and the group which had not, the ratio of bacitracin to penicillin in the first group is 35 to 1 (see Table VIIb), while in the latter group the ratio is less than 4 to 1 (see Table VIIc). This would seem to indicate clearly that many organisms had built up a resistance to penicillin in response to treatment with it. A comparison of the acute and chronic groups in this regard shows that there is no essential difference, so it is not a feature of the passage of time alone.

In the appraisal of any antibiotic, of greatest interest are the cases which respond promptly, dramatically, "brilliantly," "miraculously" and in which there is no doubt in anyone's mind that the drug has been a potent factor in the control of the infection. But perhaps from a scientific point of view of equal importance are those cases in which the effect of the drug is nil. Among the questionable cases there is room for argument as to whether the drug helped or not, but not among those in the column in which there was obviously no effect. There were 61 of these cases and an attempt has been made to analyze the reasons for failure. In 8 of them the patient was moribund and perhaps they should not be included in the series, but the authors wish to point out that treatment with bacitracin was never refused in order to bolster statistics. It was sometimes given when it was obvious that any treatment was utterly hopeless. There were 11 cases in which the causative organism proved to be resistant to bacitracin. The 7 cases of endocarditis had all had prolonged and unsuccessful treatment with large doses of other antibacterial agents. Successful treatment of such cases will have to await the further purification of bacitracin. In 8 cases treatment with bacitracin was discontinued because of some evidence of nephrotoxicity, and in one it was stopped because the patient complained of the pain of injection. In some of the remaining cases it was obvious that the nature of the illness, the extent of the lesion, the degree of tissue necrosis and the inaccessibility of the infection to the drug seemed to explain the failure, while in the remainder the cause of failure was not apparent.

The following brief outlines of case histories will illustrate the results which were obtained

during the three phases of this study and will serve to emphasize what has been mentioned above, that during the first phase while we were using the surface growth material the evidences of nephrotoxicity were inconsequential. In the second phase, when we were using the earlier product made in the deep tanks, the nephrotoxicity was disturbing. In the last phase, while we were using the material which meets a Food and Drug Administration toxicity test of LD50/500 units for a 20 gram mouse, our confidence in its efficacy and safety has been largely restored.

CASES ILLUSTRATING THE RESULTS OBTAINED WITH "SURFACE GROWTH" BACITRACIN DURING THE FIRST PHASE OF THE STUDY

CASE 1. J. B., male, aged 43 years. Deep abscess of thigh. Series No. 1007.

Three weeks before admission this patient was taken ill with chills and fever and generalized aches and pains. Two days later a tender mass appeared in the upper inner area of the left thigh. He was given penicillin with temporary subsidence of the mass but then it recurred and did not respond to further treatment with penicillin. On admission to the hospital he was given 15,000 units of bacitracin every 6 hours with prompt improvement, subsidence of the mass, and freedom of movement without pain. However, the mass did not completely disappear. Improvement came to a standstill and temperature and blood count remained high. The mass was explored and found to be a deep abscess around the femoral vessels which yielded on culture a hemolytic streptococcus. The dose was increased to 30,000 units and the abscess cavity was irrigated daily with bacitracin solution containing 1,000 units per cubic centimeter. Exudation in the cavity decreased rapidly and on the fifth day of local treatment the wound was closed with sutures and it healed by primary union. The stitches were removed on the sixth day after suturing. Systemic bacitracin was stopped on the following day and he was allowed to walk around. Two days later he was on schedule to leave the hospital, but his temperature rose slightly and pain recurred in the thigh. He was put back to bed and systemic bacitracin again administered, 30,000 units every 6 hours with immediate improvement. Residual induration in the thigh, however, indicated aspiration, which yielded 25 cubic centimeters of pus. This was replaced by 2,500 units of bacitracin. Daily aspiration of pus and instillation of bacitracin caused a rapid subsidence of the process, and no treatment was needed after the fourth day. This patient has been followed over a period of 28 months, and there has been no evidence of recurrence of the process nor symptoms or signs of nephrotoxicity.

CASE 2. O. C., female, aged 46 years. Cellulitis of arm. Series No. 1005.

Four months before admission, a hormone injection in the right arm was followed by infection. This was not controlled by incision. The cellulitis gradually spread to involve the whole arm. A second incision on the inner surface also failed. The whole circumference of the arm from elbow to shoulder was red and markedly swollen. Beside the two incisions which had never healed, 5 spontaneous sinuses had developed. Culture revealed a hemolytic streptococcus susceptible to penicillin and bacitracin and a hemolytic Staphylococcus aureus resistant to penicillin but susceptible to bacitracin. With intramuscular 15,000 units of bacitracin every 6 hours, the sinuses began to close after 48 hours. In 12 days healing had occurred and surgical treatment was obviated.

CASE 3. A. W., female, aged 32 years. Progressive postoperative bacterial synergistic gangrene. Series No. 1013.

This was a typical case of this disease of 4 months' duration following a hysterectomy, which did not respond to penicillin, streptomycin, sulfadiazine, and many forms of local treatment, including a trench operation. The infection jumped over the trench and spread out into the flanks and down both thighs. Cultures showed a mixture of organisms, pyocyaneus, proteus and a hemolytic Staphylococcus aureus susceptible to bacitracin but resistant to penicillin. The microaerophilic nonhemolytic streptococcus was not found, probably being masked by the proteus and pyocyaneus, which may have been responsible for the failure of penicillin to control the infection. In 48 hours, after receiving intramuscular bacitracin in a dosage of 20,000 units every 6 hours, the spread of the infection ceased and the gangrenous margin had begun to separate spontaneously. This was completed in 72 hours and epithelium very rapidly spread over all the surface from remnants of the hair follicles and sweat glands. The proteus-pyocyaneus factors of the infection were controlled by the local application of 0.25 per cent parachlorophenol solution combined with bacitracin in a concentration of 500 units per cubic centimeter. Final epithelization was favored by a 2 per cent oxyquinoline and 5 per cent scarlet red ointment. Healing was complete in 8 weeks without the necessity for excision or skin grafting.

CASE 4. N. A., male, aged 22 years. Infected operation wound with cellulitis of back. Series No. 1024.

A sebaceous cyst was removed from the lower posterior chest and within 12 hours a red hot infection developed which spread over all the back and left flank. He was very toxic and the infection did not respond to three doses of 500,000 units of penicillin in oil at 12 hour intervals with 50,000 units by mouth every 2 hours. The cultures yielded a group A hemolytic streptococcus and a coagulase positive Staphylococcus aureus, both sensitive to both penicillin and bacitracin. It has been observed before that this

combination may resist penicillin treatment even though the individual organisms in pure culture are susceptible. He was given 20,000 units of bacitracin every 6 hours. The toxicity promptly disappeared and within 12 hours his temperature fell to normal, the cellulitis melted away and the wound went on to rapid healing.

CASE 5. V. H., male, aged 24 years. War wound with suppurative osteomyelitis of the stump of the femur. Series No. 1023.

A Marine lieutenant had received a compound fracture of the femur, produced by a dumdum bullet at Iwo Jima. He was given penicillin and sulfadiazine, but developed an infection which failed to respond to surgical drainage and the further administration of antibacterial agents. He was transported to Pearl Harbor, then to San Francisco, and to Chelsea, Massachusetts. In each place there was a flare-up of infection, treated by multiple incisions for drainage. Finally, at Chelsea amputation was done to save the patient's life, but the stump became infected. A transfer to Philadelphia and further incisions and more drugs failed to control the infection. After 3 years, draining sinuses were still present at the end and on the lateral surface of the stump. Cultures revealed a Staphylococcus aureus susceptible to bacitracin but resistant to penicillin, and Bacillus proteus.

On admission the x-ray films showed residual foreign bodies and osteomyelitis of the stump. He was given intramuscular bacitracin in a dosage of 18,000 units every 6 hours. After 2 days the dose was increased to 33,000 units. On the third day he was operated upon. Most of the metal and all of the diseased bone were removed. Bacitracin was instilled locally into the bone cavity by means of plastic catheters. There were also two separate abscess cavities on the inner side of the thigh, which were drained through separate small counter-incisions and bacitracin was instilled into these cavities. The catheters were removed on the fourth day. The lateral wound granulated rapidly and on the seventeenth day the granulations were covered with pinch grafts. Healing was complete in a month. During this time the patient gave no evidence of renal toxicity from a daily dose of 120,000 units a day, except for a little albumin and a few casts lasting 3 days in the early days of the treatment. (See Table VIII. This table is typical of cases treated in the "first phase" of the study.) A year after the above treatment the pebbly area of skin was excised and a primary closure of the wound was successful with the aid of systemic bacitracin for 10 days.

TABLE VIII.—URINE CHART FOR CASE 5

Date 1948	c.c. Urine 24 hrs.	Dosage units	pH	NPN mgm.%	Alb.	Casts
1-29	2050		7	25	o	o
1-31	2300	132,000	6.5		st	o
2-1		99,000	6		ht	few
2-2			7		t	few
2-3			7		o	rare
2-4	1900	132,000	7		o	o
2-5	2100	132,000	7		spt	o
2-6	1500		6.5		o	o
2-7	1800	120,000	6.5		o	o
2-8	1500	120,000	6.5		o	o
2-9	1500	120,000	7		o	o
2-10	1650	120,000	7		o	o
2-11	1900	120,000	7.5		o	o
2-12	2750	120,000	7.5		o	o
2-13	2400	120,000	6		o	o
2-14	2000	120,000	6.5		o	o
2-15	1900	120,000	7		o	o
2-16	2200	120,000	6		o	o
2-17	1800	120,000	7.5		o	o
2-18	1500	120,000	6.5		o	o
2-19	2100	120,000	7.5		o	o
2-20	2400	120,000	7.5		o	o
2-21	2630	120,000	6		spt	o
2-22	980	120,000	7.5		o	o
2-24	2150	120,000	7.5		o	o
2-25	2050	120,000	7.5		o	o
2-26	1400	120,000	7		st	o
2-27	2300	120,000	7.5		o	o
2-28	2000	120,000	7.5		o	o
2-29	1800	120,000	7.5		o	o
3-3				23		

This table shows that a daily dose of 120,000 units of the surface growth bacitracin for over a month was well tolerated and resulted in minimal and only transient evidence of kidney irritation. This was typical of all but 1 or 2 cases during the first phase of the study.
spt, Smallest possible trace; st, slight trace; t, trace; ht, heavy trace.

CASE 6. J. L., male, aged 27 years. Osteomyelitis of the radius following bone graft operation. Series No. 1027.

This was an American infantry officer wounded in Germany by a rifle bullet through the left forearm, both thighs, and the scrotum. He was captured by the Germans and recaptured by the Russians. He was finally evacuated through Odessa. By that time all wounds had healed. He was sent to an American army hospital where because of the shortening of the radius, a bone graft was introduced. The wound healed without apparent infection, but a month later an abscess formed and came to the surface. It was surgically drained and a number of small sequestra were found and others came out later. The wound then healed slowly, but flared up again a week before admission to the hospital. X-ray films revealed osteomyelitis around the lower screws (see Fig. 1). These screws and the infected bone around them

were removed. The cultures showed a Staphylococcus aureus susceptible to bacitracin but resistant to penicillin. He was given 20,000 units of bacitracin every 6 hours for 11 days and it was also instilled locally into the wound. This gradually filled with granulations and healed. During the course of treatment the patient had nausea and vomiting, but this did not interfere with treatment. There was albumin in the urine and a moderate transient rise in nonprotein nitrogen.

CASE 7. E. W., male, aged 24 years. Actinomycosis of hand. Series No. 1016.

This patient developed an actinomycosis of the hand in a wound from a tooth injury. This steadily increased in size over a period of 11 months. Actinomyces bovis was cultured from the wound as well as Staphylococcus aureus susceptible to bacitracin but resistant to penicillin. He was put on intramuscular bacitracin in a dosage of 20,000 units every 6 hours for 3 days. On the third day the swelling began to subside. The dose was doubled, but because of some nausea and vomiting after 3 days it was reduced to the original dosage. After 10 days the patient insisted upon leaving the hospital because of certain home responsibilities and he did not come back for a month, at which time it was found that the swelling had increased. An x-ray examination revealed that the third metacarpal bone was involved in the process (see Fig. 2). It was decided that the best chance for recovery would be an excision of the local lesion and a continuation of drug treatment. He was therefore given 22,000 units of bacitracin every 6 hours. The diseased tissue was removed. This included the third and fourth fingers and their corresponding metacarpal bones and a portion of the os magnum. The wound was closed primarily with a small plastic catheter placed in the web, through which bacitracin was instilled locally for 3 or 4 days. The catheter was then removed. The wound healed by primary intention and excellent function of the hand was restored. There has been no recurrence of the infection during 18 months.

CASE 8. M. F., female, aged 32 years. Postabortal sepsis. Series No. 1030.

Five days before admission to the study, this patient had been relieved of a threatened abortion by a dilatation and curettage. Her temperature rapidly rose to 106 degrees, where it stayed for 3 days in spite of sulfadiazine, penicillin, and streptomycin. There was a prompt response to bacitracin in a dosage of 20,000 units every 6 hours. Within 4 hours the patient began to have a sense of well being. All attending doctors believed that bacitracin saved her life. Aerobic cultures which were made of the cervical discharge showed no growth, but the infecting organism was believed to be an anaerobic streptococcus.

CASE 9. L. S., male, aged 58 years. Bronchiectasis. Series No. 6010.

This patient had an 8 year history of bronchiectasis and emphysema which had failed to respond to penicillin and sulfadiazine. The penicillin caused a severe reaction and it had to be discontinued. Cultures from the sputum yielded a group A hemolytic streptococcus and a nonhemolytic streptococcus which were susceptible to both penicillin and bacitracin. He was given 22,000 units of bacitracin every 6 hours for a period of 2 weeks. During the period of treatment the sputum decreased from 120 cubic centimeters to 20 cubic centimeters per day. A month later he had no purulent sputum and was able to return to work.

CASE 10. W. D., male, aged 29 years. Cellulitis following human bite. Series No. 5010.

A 2 day history of human bite, involving lacerated wounds in the soft tissues of the chest wall and the distal phalanx of the index finger, yielding on culture a mixture of organisms, with swelling, redness, pain, tenderness and fever, responding dramatically to systemic bacitracin therapy in a dosage of 9,900 units every 6 hours for 4 days. Within 24 hours practically all of the tenderness and pain disappeared and the cellulitis had subsided.

CASE 11. E. R., male, aged 6 years. Cellulitis of leg. Series No. 5029.

This patient had an extensive cellulitis of the leg with inguinal lymphadenitis and a high fever, as well as redness, pain, tenderness, and a blistering of the skin. The response to treatment with bacitracin with 19,000 units every 6 hours was dramatic with complete clearing of the lesion in 3 days. The cultures yielded a highly sensitive gram negative bacillus which was resistant to penicillin but susceptible to bacitracin. The patient left the hospital after a period of 6 days.

CASE 12. G. S., male, aged 4 years. Cellulitis of leg. Series No. 5032.

This patient came into the hospital with a history of very rapidly developing cellulitis of the leg all the way up from the ankle to the knee with a severe toxemia and inguinal adenitis. There was swelling, redness, pain, and a fever of 105.6 degrees, all of which subsided dramatically within 48 hours following the administration of 20,000 units of bacitracin every 6 hours.

CASE 13. A. G., female, aged 67 years. Postradiation cellulitis of chest wall. Series No. 5030.

This patient had had a radical mastectomy 2 months previously and had received a full course of postoperative irradiation, following which she developed an extensive cellulitis of the entire left half of the chest wall, front and back. The swelling extended down on to the abdominal wall and down the arm to the elbow. She was very toxic, running a high fever. She was given 40,000 units of bacitracin every 6 hours. Toxic symptoms disappeared in 48 hours and the temperature reached normal on the third day. Before treatment began the blood urea was 30.8 milligrams per cent and during the treatment it went up to 38.4 milligrams per cent. The urine showed hyaline and granular casts before bacitracin and a 1 plus albumin with an occasional granular cast appearing during treatment, but these promptly disappeared.

CASES ILLUSTRATING THE RESULTS OBTAINED WITH "EARLY DEEP TANK BACITRACIN" DURING THE SECOND PHASE OF THE STUDY

CASE 14. H. B., male, aged 35 years. Cellulitis of neck. Series No. 1043.

Two days before admission this patient developed an infection on the front of the neck over the larynx. He was given 500,000 units of penicillin, but the infection continued to spread during the night until there was a zone of cellulitis all around the front of the neck extending down to the anterior chest with a small opening through the skin over the larynx where some necrotic tissue was seen. Penicillin treatment was continued and 40,000 units of penicillin were injected in the local area without improvement. Because of the rapid spread of the infection, it was thought advisable to start him off with a large dose of bacitracin and 38,000 units from lot No. 480210 were given and repeated twice at 4 hour intervals. His temperature began to come down after the third dose, so the interval was increased to 5 hours for the fourth dose and to 6 hours for the fifth dose. Thereafter it was continued every 6 hours. On the third day the cellulitis in the neck had almost entirely subsided, indicating a favorable response to bacitracin. No cultures were taken, but the condition behaved like a hemolytic streptococcal cellulitis. However, on the third day he became nauseated and vomited several times, so bacitracin was stopped after 9 doses with a total of 342,000 units. On the third day his urine showed 2 plus albumin and a few red and white blood cells. On the fourth day this had increased to 3 plus albumin, but he felt well enough to go home. However, after his return home he complained of nausea, vomiting, and lethargy. He then reported that he had voided only a few ounces of urine. When these symptoms continued for 2 days, it was thought best that he should return to the hospital. However, with expectant treatment his urinary output gradually increased until on the eighth day he was voiding over a liter and on the tenth day it reached 2,340 cubic centimeters. The nonprotein nitrogen reached a peak of 117 milligrams per cent on the day after his readmission to the hospital, but on the ninth day it was down to 43 milligrams per cent and he left the hospital on the twentieth day with all of his renal function restored to normal. Later examinations have shown no residual evidences of kidney damage. (Table IX illustrates the study of his renal function.)

CASE 15. W. D., male, aged 18 years. Cellulitis of neck. Series No. 1047.

Four days before admission to the clinic the patient developed two furuncles on the chin. Penicillin was injected locally in a dosage of 2,000 units per cubic centimeter and on the following day some necrotic tissue was extruded from each lesion. This local treatment was continued and the redness and swelling subsided slightly but on the ninth day of the infection, swelling, redness and induration recurred and rapidly increased. Penicillin was then given

Fig. 1, left. Roentgenogram of Case 6 showing osteomyelitis around the lower screw holes in the bone graft.

Fig. 2. Roentgenogram of Case 7 showing osteomyelitis of the third metacarpal bone in actinomycosis of the hand.

intramuscularly, but this was followed by an itching rash over the neck and the upper part of the trunk, and the local lesions showed no evidence of improvement. The patient then stated that 6 months before he had had two injections of penicillin without any reaction and this was thought to be a sensitivity response. Cultures of the wounds showed a coagulase positive hemolytic Staphylococcus aureus, which was susceptible to both penicillin and bacitracin. He was given bacitracin in a dosage of 20,000 units from lot No. 480212 every 6 hours and the local wounds were irrigated with bacitracin solution containing 500 units per cubic centimeter. The next day he was definitely better. The swelling had decreased. The improvement during the next day was dramatic indeed and on the following day he was so much better that he was allowed to go home. During his hospitalization the urine did not show any albumin and the blood urea nitrogen remained at the low level of 12 milligrams per cent. The phenolsulfonphthalein was 65 per cent on the second day and 80 per cent on the fourth day. When he came to the clinic on the day after his discharge from the hospital the inflammation had further subsided, but he reported that he felt nauseated and had vomited. The urine then showed a 3 plus albumin, 4 plus glucose with clumped white cells and 5 to 6 red cells per high power field. He was admitted to the overnight ward and on the following day his blood urea nitrogen was 21 milligrams per cent, but the albumin, glucose, and cellular elements began to decline. During the following day he continued to improve, his appetite returned and his urine was in good

TABLE IX.—URINE CHART FOR CASE 14

Date 1948	c.c. Urine 24 hrs.	pH	Sp. gr.	Alb.	Microscopic examination of centrifuged specimen				BUN or NPN mgm.%	PSP	Dosage units
					WBC	RBC	Epith.	Casts			
4–22				o	o	o	o	o			38,000
4–23		ac.	1020	o	o	o	o	o			190,000
4–24	1350	6	1016	2+	6–8	1–2	occ.	o			104,000
4–25			1030	3+	5–6	1–2		2–3			stopped
4–26	2100	7		3+	5–6	o	3–4	5–6	NPN		
4–27	<100	ac.		2+	many	6–8		8–9	69		
4–28	<100	ac.	1008	4+	5–10	1–3		25	117		
4–29	110	ac.	1010	3+	15	15–20	5–6		BUN		
4–30	180	5	1010	3+	15	4–5		1–3	124		
5–1	220	5.5	1008	2+	3–5	3–4		1–2	127		
5–2	345	5.5	1010	2+	3–5	occ.		occ.			
5–3	550	6	1010	2+	3–5	occ.		occ.	100		
5–4	375	5.5	1010	2+	10–15	10–12		10	77		
5–5	1135	5.5	1010	2+	3–5	occ.		2–3	100		
5–6		5.5	1008	1+	3–5	2–3		2–3	43		
5–7	2340	6	1010	1+	3–5	1–2		o	110		
5–10	1700	6	1010	1+	many	occ.		4–5	77		
5–13	2300	6	1008	1+	5–10	1–2		o	60	30	
5–15	1500		1010								
5–17									30		
5–26				o					NPN		
5–28									30		
6–15			1028	o	rare	o	o	o		40	

The table shows the changes in the albumin and microscopic picture, the high blood urea nitrogen and low specific gravity following the administration of one of the most toxic lots. Restoration, however, was complete in a month.

volume. The albumin fell to 1 plus, glucose was negative, and the red blood cells were rare. Four days after discharge the blood urea nitrogen had returned to normal.

CASE 16. J. R., male, aged 21 years. Paronychia of toe, cellulitis of foot and inguinal lymphadenitis. Series No. 7004.

Four days before admission this patient developed a paronychia of the large toe with a rapid spread of redness, swelling, pain and tenderness on the dorsum of the foot and with tender inguinal lymph glands. Cultures showed a hemolytic streptococcus sensitive to both penicillin and bacitracin and a coagulase positive Staphylococcus aureus sensitive to bacitracin but resistant to penicillin. He was put on 20,000 units of bacitracin from lot No. 471212, and the nail was removed. There was a prompt clinical response within 72 hours. On the fifth day the nonprotein nitrogen rose from an initial level of 32 milligrams per cent to 42 milligrams per cent and the phenolsulfonphthalein fell from 70 per cent to 54 per cent. Renal cells were still present on the thirteenth day, but thereafter signs of nephrotoxicity cleared.

CASE 17. M. C., male, aged 17 years. Cellulitis of the hand and arm with axillary lymphadenitis. Series No. 7011.

Six days before admission this patient had an accidental avulsion of the skin over the dorsum of the right hand and the wound promptly became red, swollen, tender, and obviously infected. Two days before admission a painful lump developed in the axilla with red streaks coursing up from the area of infection on the hand. He was given bacitracin in a dosage of 11,800 units from lot No. 471231 every 6 hours. The cultures showed hemolytic streptococcus, susceptible to both penicillin and bacitracin, and coagulase negative Staphylococcus aureus susceptible to bacitracin and resistant to penicillin. The infection promptly subsided and resolved completely after 96 hours. On the fourth day of treatment, casts and renal cells appeared in the urine, but there were no red cells. The nonprotein nitrogen, starting with 39.9 milligrams per cent before bacitracin, rose quickly to 61.5 milligrams per cent on the fourth day. The phenolsulfonphthalein fell slightly during this time. The patient left the hospital on the fourth

day with no complaints except slight anorexia and malaise. After leaving the hospital he steadily improved and soon went back to active duty in the Army without any evidence of any kidney damage.

CASES ILLUSTRATING THE RESULTS OBTAINED DURING THE THIRD PHASE OF THE STUDY WITH "LATER DEEP TANK" BACITRACIN MEETING THE FOOD AND DRUG ADMINISTRATION TOXICITY TEST OF LD 50/500

CASE 18. S. L., female, aged 79 years. Suppurative arthritis of hip after arthroplasty. Series No. 1070.

Three years before admission this patient had fallen and broken her hip. She was taken to a local hospital and the fracture was pinned, but this treatment was not successful and an arthrotomy was performed. The wound became infected and continued to drain for a long time through the operative site and a spontaneous sinus developed on the inner surface of the thigh. This sinus drained profusely over a period of 3 years. Culture then yielded a Staphylococcus aureus susceptible to bacitracin but resistant to penicillin. An x-ray plate taken after lipiodol injection revealed that there was an abscess cavity extending upward from the sinus opening into the hip joint where there was a large fragment of the femoral head (see Fig. 3). Bacitracin was instilled through the sinus for several days and then through an anterior approach the head of the femur was removed from the hip joint. She was treated intramuscularly with 10,000 units of bacitracin every 6 hours and the sinus was irrigated daily with a solution of bacitracin containing 500 units per cubic centimeter, without any evidence of toxicity except light nausea. The anterior wound healed rapidly and after 5 weeks the sinus in the groin closed and has remained healed. There has been a steady increase in the function of walking, with the infection apparently completely arrested.

Fig. 3. Lipiodol injection of a suppurative arthritis of the hip in Case 18 following arthroplasty for a comminuted fracture. Part of the head of the femur is seen acting as a sequestrum.

CASE 19. P. W., male, aged 13 years. Staphylococcus septicemia with acute osteomyelitis of the femur. Series No. 1066.

This boy had been playing soccer on the day before admission and had fallen down a number of times. He awoke early the next morning complaining of pain in the region of the left hip. He felt nauseated and vomited and 3 hours later had a short chill. His temperature during the day gradually rose to 103.6 degrees and he appeared very toxic and in great pain. There was tenderness well localized to the posterior region of the hip joint, but the joint itself was free, although extremes of flexion and extension caused pain. He was brought into the hospital and a blood culture was taken. He was given 100,000 units of penicillin and 50,000 units every 3 hours during the night. The next morning his temperature was 104 degrees. Tenderness was still present, so the dosage of penicillin was increased to 100,000 units every 3 hours. On the third day he seemed a little better. There was less tenderness and muscle spasm, but with the diagnosis and the organism still in doubt, he was given sulfadiazine along with the penicillin, but together they failed to control the infection. On the fourth day his pain, tenderness, and Kernig's sign reappeared, indicating a reactivity of the process. The blood cultures taken on admission and on the first day after admission both grew out on the fourth day revealing a coagulase positive hemolytic Staphylococcus aureus. It was then obvious that he had a staphylococcus septicemia with an osteomyelitis probably of the neck of the femur. On the fourth day when the nature of the organism was known, sulfadiazine was stopped and he was given bacitracin in a dosage of 200 units per kilogram of body weight (5,250 units) every 6 hours. Blood culture taken on that day showed no growth. On the fifth day the bacitracin dosage was doubled. That day the sensitivity test revealed that the organism was resistant to penicillin but susceptible to bacitracin, explaining the failure of penicillin to bring about the expected prompt response. However, it was demonstrated that there was a synergism between bacitracin and penicillin, which permitted 1/10 of the growth inhibiting dose of one, plus 1/32 of the growth inhibiting dose of the other to prevent

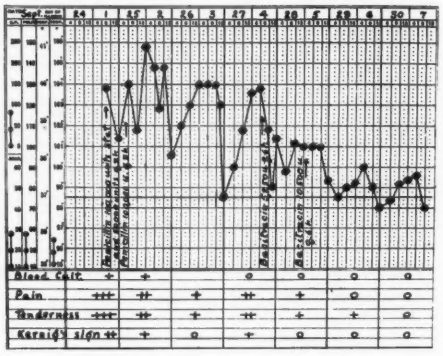

Fig. 4. Temperature curve of Case 19 showing failure of penicillin to control the infection and resolution when bacitracin was added to the therapy.

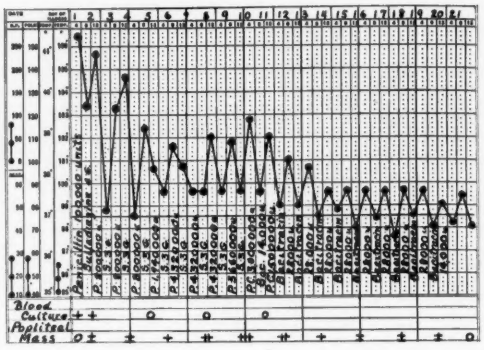

Fig. 5. Temperature curve of Case 21 showing rising temperature and increasing mass in popliteal space not controlled by penicillin but responding to bacitracin.

the growth of the organism in vitro. Thereafter all symptoms and signs rapidly subsided (Fig. 4). During this treatment the nonprotein nitrogen rose from 30 to 49 milligrams per cent, but with continued treatment it came down again to 32 milligrams per cent at the end of treatment and thereafter dropped back to normal (see Table X for a résumé of his toxicity studies). There were no clinical symptoms of toxicity and this rise in nonprotein nitrogen was not sufficiently alarming to warrant cessation of treatment. It is likely that in this case the favorable response was due to a synergistic action between the two antibiotics. On the tenth day the x-ray film revealed a suggestive area of beginning rarefaction in the neck of the femur, but on subsequent x-ray films this disappeared. However, the clinical diagnosis was unmistakable.

CASE 20. S. T., female, aged 62 years. Post-craniotomy wound infection with subdural abscess. Series No. 1100.

Three weeks before treatment began, a cortical ablation had been done of the right frontal lobe through an osteoplastic craniotomy for a depressive type of schizophrenic psychosis. Postoperatively she received 50,000 units of penicillin every 3 hours for 8 days and 300,000 units of duracillin a day for 7 days. Two days after stopping this treatment the patient became drowsy and fluctuation of the scalp

TABLE X.—URINE CHART FOR CASE 19

Date 1948	c.c. Urine 24 hrs.	pH	Sp. gr.	Alb.	Microscopic examination of centrifuged specimen				NPN mgm.%	PSP	Dosage units
					WBC	RBC	Epith.	Casts			
9–26			1010	o							
9–27									32	45	5,250
9–28		7	1022	o	o	o	o	o			31,500
9–29	950	7	1028	o	1–3	o	o	o	36	85	42,000
9–30	1300	7.5	1026	tr.	3–5	o	3–5	occ.	40		42,000
10–1	1800	7.5	1025	3+	5–6	o	4–6	occ.	49	55	42,000
10–2	1400	7	1020	3+	5–6	occ.	6–8	1–2	43		42,000
10–3		6	1016	3+	5–6	o	5–6	1–3			42,000
10–4		6.5	1017	3+	2–4	o	5–6	occ.		75	42,000
10–5	1960	6.5	1019	3+	3–4	o	6–8	2–4	42		42,000
10–6	1500	6.5	1022	1+	5–6	o	3–5	2–4		60	42,000
10–7	1400	7	1020	1+	2–3	o	1–3	1–3	32		31,500
10–8		7.5	1027	1+	2–3	o	1–3	rare		60	stopped
11–17		6	1025	o	rare	o	o	o	29		

This table shows the moderate but transient evidence of kidney irritation with rise and fall of nonprotein nitrogen during treatment.

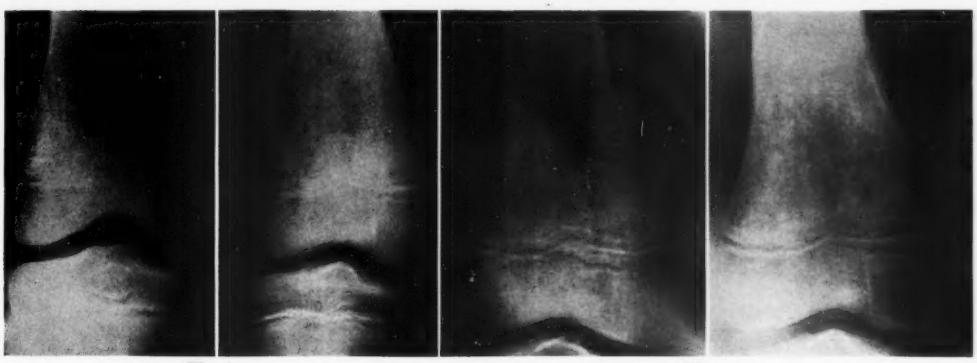

Fig. 6.

Fig. 6. Roentgenogram of Case 21 showing progressive breakdown of the bone.

Fig. 7.

Fig. 7. Later films of Case 21 showing progressive regeneration of the bone with no clinical signs or symptoms.

revealed an underlying abscess. Penicillin was increased to 150,000 units every 3 hours, but this failed to control the infection. The wound was opened and a large quantity of pus was released yielding a staphylococcus susceptible to bacitracin but resistant to penicillin. The wound was opened further and the bone flap removed. A subdural abscess was found. She was given 10,000 units of bacitracin in 10 cubic centimeters of saline instilled into the wound through a sterile catheter every 3 hours. Bacitracin was also given intramuscularly in a dosage of 10,000 units every 6 hours for a period of 10 days. The local instillation was continued for a month, the sinus at the catheter site remaining open. During this treatment the blood urea nitrogen tests remained essentially unchanged. The sinus persisted until it was re-explored and a small piece of necrotic tissue which was acting as a foreign body was removed. With a continuation of local bacitracin the sinus promptly closed.

CASE 21. W. R., male, aged 10 years. Staphylococcus aureus septicemia with acute osteomyelitis of the femur. Series No. 1039.

This boy had a sudden onset of pain in the popliteal space of the left leg followed by inability to walk and high fever. On admission to the hospital the next day his temperature was 106 degrees. He had diffuse pain and tenderness in the region of the lower end of the left femur. He was immediately put on penicillin in a dosage of 100,000 units every 3 hours and sulfadiazine 0.5 grams every 4 hours. His temperature stayed up for 24 hours and then came down toward normal, but then rose again and reached 104.4 degrees on the fourth day. During this time there was a slow but steady development of a mass in the popliteal space. Blood culture on admission showed a hemolytic Staphylococcus aureus resistant to penicillin but susceptible to bacitracin. Therefore all other treatment was stopped and he was given bacitracin in a dosage of 400 units per kilogram of body weight. It was thought that the popliteal mass was an abscess which would require drainage, but following bacitracin treatment the mass steadily decreased in size, the function of the leg rapidly improved and he was soon able to return home, having shown no evidence of renal toxicity. A series of x-ray films showed an area of osteomyelitis in the lower end of the femur with a progressive breakdown of bony tissue, then a standstill and a gradual restoration (see Fig. 5). In this case the penicillin plus the sulfadiazine controlled the septicemia, but they could not control the local process. Nevertheless bacitracin stopped its progress and caused its steady resolution. He has been perfectly well for 6 months so far. Figure 6 shows progressive breakdown and Figure 7 regeneration of bone.

CASE 22. M. B., female, aged 6 weeks. Staphylococcus septicemia and meningitis with metastases in lungs and subcutaneous tissues. Series No. 1080.

This baby was born prematurely but left the hospital after 3 weeks weighing 5 pounds. Four days after discharge the right side of the face began to swell and there was a bloody nasal discharge. She was taken to a suburban hospital where she was given penicillin and streptomycin without any appreciable effect. She was therefore brought to the Babies Hospital in New York, where the penicillin dosage was increased and where blood culture revealed the hemolytic Staphylococcus aureus septicemia and a lumbar tap revealed meningitis. The dosage of penicillin was increased and this was also given intrathecally but without effect. Streptomycin was also given intrathecally and then aureomycin was started, but all of these treatments failed to control the infection. Metastatic abscesses appeared in the back and on one hand and one foot. Several areas in the right lung field suggested a pneumonitis with early abscess formation. The baby's neck was stiff and she was semicomatose when bacitracin was called for. She was started on 400 units per kilogram of body weight every 6 hours intramuscularly. It

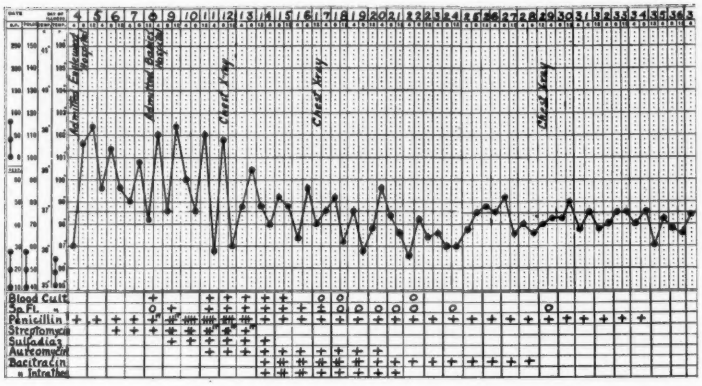

Fig. 8. Temperature curve of Case 22 showing failure of septicemia and meningitis to respond to penicillin, sulfadiazine, streptomycin, and aureomycin with prompt response when intramuscular and intrathecal bacitracin was added.

was also given intrathecally twice a day in a dosage of 500 units and it was instilled into the abscess of the face through a plastic catheter in a dosage of 500 units per cubic centimeter. Two days after beginning treatment the patient came out of her coma. The blood and spinal fluid cultures became normal on the fourth day of bacitracin treatment and thereafter she went on to a complete recovery (see Fig. 8). The incipient abscesses of the lungs resolved completely (see Figs. 9, 10). There was a moderate rise of the nonprotein nitrogen from 30 to 38 milligrams per cent, but it returned promptly to 31 milligrams per cent.

It was generally agreed that bacitracin had saved this patient's life.

CASE 23. E. R., female, aged 30 years. Pansinusitis with undermining burrowing ulcer of face and orbits. Series No. 1072.

This patient had had an infection of the bones of the face starting 5 years before as a pansinusitis which spread from the antrum up into the right orbit, requiring the removal of the eye. Gradually the process then spread to the left orbit. All of the small bones of the face were involved in the destruction. She was given several series of penicillin treatments without any effect and also a long period of aureomycin. This case had many of the features of undermining burrowing ulcer. However, the characteristic microaerophilic hemolytic streptococcus was not found. The only organism constantly present was a Staphylococcus aureus, susceptible to bacitracin but resistant to penicillin. (Fig. 11 shows the lesion at this time.) Bacitracin was then started in a dosage of 10,000 units every 6 hours. It was also used locally in the form of an ointment and a solution which was applied on gauze packing. It was obvious within a few days that the spread of the infection had stopped. After a month of treatment with only partial improvement because the infection was still active in the left orbit and beneath the eyelids, it was decided after 50 days of bacitracin treatment to remove all of the diseased tissue and to cut back the undermined margins so as to permit a more complete contact of the medication with the infected tissue. At the same time the systemic dosage of bacitracin was increased to 20,000 units every 6 hours. Thereafter the whole wound cleaned up with remarkable rapidity, new skin grew in from the margins and on the twenty-first day the entire area was covered with pinch grafts. These took everywhere except in several small areas where there was residual nasal mucosa (see Fig. 12). These areas were then curetted and the defects covered with similar grafts. These also took satisfactorily and the area was soon completely covered.

This patient has the record for prolonged treatment with bacitracin. For 50 days she received 40,000 units a day and for 85 days, 80,000 units a day. The total systemic bacitracin was 9,360,000 units. About 800,000 units were used locally during the course of treatment. The nonprotein nitrogen stayed at a remarkably constant level, being 23 milligrams per cent before beginning bacitracin and 28 milligrams per cent at the end of treatment. This is unquestionably a case in which the life of the patient was saved and the infection brought under control by bacitracin. Standard doses of bacitracin were continued for almost 5 months with little or no evidence of kidney damage.

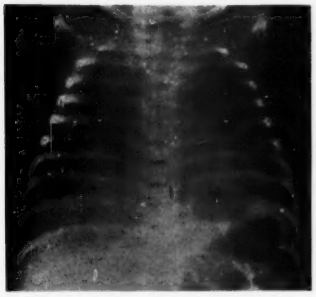

Fig. 9. Roentgenogram of Case 22 showing metastatic abscesses of the lungs before bacitracin therapy.

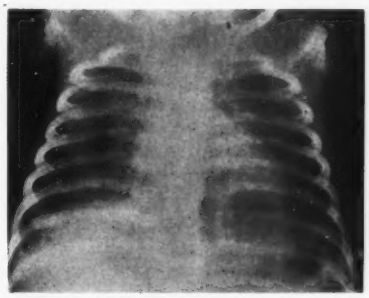

Fig. 10. Roentgenogram of Case 22 showing clearing of lung lesions after bacitracin.

CASE 24. D. M., male, aged 60. Gangrenous ulcer of back, flank, and buttock. Series No. 1092.

Five weeks before admission this patient developed a pleuritic pain in his left chest, which was strapped with broad adhesive to which his skin was sensitive. The skin became blistered like a second degree burn and the whole area then became infected with a very peculiar type of gangrene. This spread rapidly all over the back, into the left flank and down on the buttock. The infection failed to respond to penicillin, sulfadiazine, and streptomycin. (Fig. 13 shows the lesion when it was first seen by F.L.M.) He was given bacitracin in a dosage of 10,000 units every 6 hours and in 48 hours it was obvious that the spread of the infection had come to a standstill. He was brought to Presbyterian Hospital in New York from a suburban hospital and the dosage of bacitracin was doubled. There was moderate but transient evidence of kidney irritation, but no significant rise in nonprotein nitrogen. The gangrenous tissue was excised and on the tenth day two-thirds of the area was covered with skin grafts, and 10 days later the remainder. There was an almost complete take of these grafts and soon they grew out epithelium from the margins and rapidly fused together (see Figs. 14 and 15). His recovery, however, was complicated by the development of two pressure sores, which occurred during the immobilization period after the grafting. The cultures yielded not only a hemolytic Staphylococcus aureus and nonhemolytic streptococcus, which were resistant to penicillin but susceptible to bacitracin, but also an Aerobacter aerogenes and later both proteus and pyocyaneus were recovered from the large area. The staphylococcus and streptococcus were brought under control by bacitracin, the proteus by parachlorophenol and the pyocyaneus by sulfamylon.

Everyone was impressed by the rapid control of the infection with bacitracin and believes that this saved the patient's life.

CASE 25. M. B., female, aged 34 years. Progressive postoperative bacterial synergistic gangrene. Series No. 1101.

This patient was admitted to a suburban hospital in the early stages of labor, but after 16 hours there was no progress and a cesarean section was performed. The patient was given 60,000 units of penicillin prophylactically and 2 grams of sulfanilamide crystals were sprinkled throughout the wound, which was then closed with silk stay sutures protected by rubber tubing. Forty thousand units of penicillin were given every 3 hours for 6 days and 1 gram of sulfadiazine was given every 4 hours for 3 days. On the eighth day, in spite of these antibacterial agents, the wound revealed an infection with redness, swelling, and small vesicles which gradually developed into bullae, evidently starting around the retention sutures.

At this time the whole wound became inflamed with areas of dusky skin somewhat raised from the surface, indicative of the early stages of bacterial synergistic gangrene. Cultures were taken which revealed the microaerophilic nonhemolytic streptococcus, Staphylococcus aureus, and Escherichia coli. The stay sutures were removed. The patient was put on bacitracin in a dosage of 10,000 units every 6 hours and it was also applied locally on wet com-

Fig. 11. Fig. 12.

Fig. 11. Progressive destruction of the eyes and small bones of the face in Case 23 up to the time of bacitracin treatment.

Fig. 12. Relatively prompt control of the infection in Case 23 by excision of undermined margins followed by systemic and local bacitracin permitting successful skin grafting on the 21st day.

Fig. 13. The extent and nature of the infection in Case 24 before treatment with bacitracin.

presses in a concentration of 500 units per cubic centimeter. Within 48 hours the spread of the infection ceased and the whole process came under control. Thereafter resolution was rapid without any necrosis of tissue.

It was generally recognized that the early diagnosis and the early administration of bacitracin completely controlled the infection and saved the patient from the development of extensive gangrene, after prophylactic penicillin, sulfadiazine, and streptomycin failed to do so.

CASE 26. G. B., male, aged 39 years. Cellulitis of the scalp. Series No. 2022.

Four days before admission this patient was hit on the head with a brick. Three days later he noted swelling of the scalp and of the tissues around his left eye. On admission to the hospital his temperature was 102 degrees and there were numerous lacerations in the left frontal region of the head, which were surrounded by a zone of cellulitis and edema extending down to the ear posteriorly and the zygoma in front. The eye was almost closed and the lids were light purplish in color. The patient was given 10,000 units of bacitracin every 3 hours for 3 days. During this time the cellulitis and edema rapidly subsided and the patient was discharged 2 days later. Although albumin appeared in the urine, the phenolsulfonephthalein filtration was normal throughout. There was a mixture of organisms, including hemolytic streptococcus, Staphylococcus aureus, Bacillus melaninogenicum, and several other organisms not fully identified.

This was considered a brilliant response of the infection to bacitracin.

CASE 27. S. D., male, aged 51 years. Cellulitis of face, diabetes. Series No. 2019.

Seven days previously this patient had squeezed a furuncle on his left cheek. Following this the area became greatly swollen and indurated. Mild diabetes had been present for about 15 years. On admission the left side of the face was involved in a severe cellulitis of the entire parotid region, the left maxillary and submental area, and an extension ran down along the sternocleidomastoid muscle, with an area of fluctuation at the site of the furuncle. This area was incised and drained. Bacitracin was given in a dosage of 10,000 units every 6 hours. The patient had a 3 plus albumin before treatment, but this decreased during therapy and the red cells, white cells, and sugar disappeared. Bacitracin was stopped after 5 days, when the temperature was normal.

This was considered an excellent response to bacitracin.

CASE 28. C. H., female, aged 13 months. Cellulitis of thigh. Series No. 5040.

Three days before admission this patient was bitten by a mosquito and the area very rapidly developed

Fig. 14. Control of infection in Case 24 and successful "postage stamp" grafts on two-thirds of denuded surface.

Fig. 15. The successful completion of the graft in Case 24.

Fig. 16.

Fig. 17.

Fig. 18.

Fig. 16. The extent and nature of the undermining burrowing ulceration in Case 29 before treatment with bacitracin.

Fig. 17. The control of the infection in Case 29 and a stage in the healing process following the administration of bacitracin therapy.

Fig. 18. The final healing in Case 29 following partially successful secondary closure.

an extensive cellulitis involving all of the anterior portion of the thigh. The patient's temperature was 104 degrees on admission to the hospital and there was swelling, redness, pain, and tenderness throughout the thigh.

She was put on 5,000 units of bacitracin every 6 hours and the temperature fell abruptly. It was almost normal on the afternoon of the first day of treatment and on the following day reached normal and remained there with complete resolution of the

Fig. 19.

Fig. 20.

Fig. 19. The extent and nature of the undermining burrowing ulcer of the thigh in Case 30.

Fig. 20. The final healing in Case 30 following bacitracin therapy.

inflammatory process. No opportunity was given for cultures. A few red and white cells appeared in the urine, but there was no albumin and no rise in the nonprotein nitrogen.

CASE 29. E. W., male, aged 70 years. Chronic undermining burrowing ulcer of abdominal wall. Series No. 5053.

Three weeks before, this patient had had an appendiceal abscess drained through a stab wound in the right flank. Immediately thereafter he developed a severe infection of the abdominal wall which spread through the subcutaneous fat down into both groins and over into the left flank with undermined skin flaps measuring 2 or 3 inches in various places. The muscle was not involved and the infection had all of the characteristics of the undermining burrowing ulcers (see Fig. 16). The microaerophilic hemolytic streptococcus was found along with several secondary contaminating organisms. The streptococcus was susceptible to bacitracin but resistant to penicillin. He was put on bacitracin in a dosage of 20,000 units every 6 hours systemically and it was used in the form of an ointment locally, containing 1,000 units per gram. Improvement was rapid and remarkable. Further extension of the infection was immediately halted and healing began almost immediately. After 10 days the wound was clean and a secondary closure was attempted, but this was only partially successful because of the secondary contaminants (see Fig. 17). However, thereafter the wound healed by secondary intention (Fig. 18) and it was the general opinion that bacitracin had saved this patient's life.

CASE 30. M. P., female, aged 41 years. Undermining burrowing ulcer of thigh. Series No. 5051.

Two weeks before admission to the hospital this patient developed a pimple on the anterior surface of the left thigh. She picked it and it began to enlarge. On admission there was a large ulcer about 4 inches in diameter on the anteromedial aspect of the left thigh in the upper third (see Fig. 19). The ulcer was excised and warm compresses were applied. Penicillin and sulfadiazine were given systemically, but there was complete failure of the ulcer to heal. Thereafter the margins of the ulcer became undermined almost up to the inguinal ligament above and to a lesser degree all around the other margins, giving the characteristic features of the chronic undermining burrowing ulcer. Intramuscular bacitracin was started in a dosage of 20,000 units every 6 hours and continued for 10 days. Bacitracin ointment was applied on fine meshed gauze. Within 24 hours improvement was abvious, and in 72 hours the whole area was covered with clean granulation tissue. The flaps thereafter rapidly became adherent and partial secondary closure and a skin graft was then done. The portion which could be sutured healed primarily and there was about an 85 per cent take of the skin graft (see Fig. 20). The urine remained normal throughout treatment and the nonprotein nitrogen fell from 17 to 12 milligrams per cent.

This was considered a most dramatic cure.

SUMMARY

1. Two hundred and seventy cases representing a wide variety of surgical infections and certain medical infections have been treated with intramuscular bacitracin over a period of 22 months by 6 different observers in different geographical areas of the country.

2. These cases have been studied in a uniform manner with careful consideration of all of the factors involved, and the results of drug treatment have been divided into 4 categories, "excellent," "good," "questionable," and "no effect." The first 2 are considered "favorable" and the last 2 "unfavorable."

3. Records of these cases have been transferred to summary sheets, which have been carefully reviewed in a central office and the data have been subjected to critical analysis.

4. About three-fifths of these cases had failed to respond to other antibacterial agents; yet 55.6 per cent then responded favorably to bacitracin. These are called "salvaged cases."

5. About two-fifths of these cases had had no previous treatment and 78.1 per cent have responded favorably to bacitracin.

6. These two groups are not comparable because the patients without previous treatment in general had been ill for a shorter period of time when bacitracin treatment was started than the patients previously treated by other methods.

7. The bacteriological studies indicate that the majority of these infections were due to a mixture of organisms.

8. The favorable results with bacitracin were obtained in these mixed infections almost as readily as in the pure infections, owing to its wide antibacterial spectrum and the absence of any inactivating substance such as penicillin has to face in penicillinase.

9. Tests for susceptibility of the organisms associated with these infections to bacitracin and penicillin, showed that the majority were susceptible to both drugs, but where there was a difference, the ratio was 10 to 1 in favor of bacitracin. The evidence seems to indicate that this is due to the fact that many of the patients had built up a resistance to penicillin during previous treatment with that drug.

10. The bacitracin used in this study was manufactured by Company A by the surface

growth method and by Company B by the deep tank method.

11. Circumstances have divided this study into 3 phases: First, the period when the patients were treated by the "surface growth bacitracin" and evidences of nephrotoxicity were minimal and inconsequential. Second, the period when patients were treated by the "early deep tank bacitracin" and evidences of nephrotoxicity were disturbing. Third, the period when patients were treated by bacitracin meeting the Food and Drug Administration toxicity test of an LD50 of 500 units for a 20 gram mouse, during which phase confidence in the efficacy and, in large measure, the safety of bacitracin has been restored.

12. Brief outlines and photographs have been presented which illustrate some of the cases of patients who have been successfully treated during these 3 phases of the study.

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THE MECHANICAL HEART-LUNG SYSTEM

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EARLY in 1948 I published the reports of the results obtained from experiments in dogs, performed by myself and staff and dealing with the use of an artificial heart with artificial lungs.

In our opinion an artificial heart must replace the organic heart temporarily; in other words it must maintain circulation throughout the body. From the interesting work of Björk it appears that with the Crafoord method only the brains of dogs are perfused. As other parts of the organism can be left without circulation for some 15 minutes, the venae cavae may then be clamped during such an interval of time so that the heart cavities become free of blood; intracardial operations are then possible.

The question arises, however, whether or not parts such as the spine, the heart muscle, or other organs can really withstand a lapse in circulation without harm. Even if that were possible, with the Crafoord method, which may be very useful for some special purposes, one is always handicapped by the time element. Our method, on the other hand, permits the maintenance of complete circulation (to the brain, to the spine, to the heart muscle, the bronchial circulation to the lungs, to the endocrine organs, to the liver, to the kidneys, etc.). Only venous blood does not enter the heart and the pulmonary circulation. The cavities of the heart are empty of blood, or nearly so.

We realize that with our broader conception of the artificial heart additional difficulties must be met. First about five times as much blood per unit of time must be oxygenated as in brain perfusion. Second, the persistence of the coronary circulation might make intracardiac operations more difficult; we have no choice, however. A prolonged lapse in coronary circulation undoubtedly will cause damage to the heart muscle (fibrillation), especially in the presence of heart weakness. If absolutely necessary the heart surgeon may interrupt the coronary circulation for a short time or he may aspirate the venous coronary blood when the right heart cavities are opened. We have accepted these difficulties readily since the great advantage of our method is that in principle we are not limited for time; we are not restricted to minutes, we may go on for hours and we hope eventually for days. The use of our heart-lung system therefore will not be restricted to operations upon the heart and perhaps some other operations, but the apparatus may possibly be used also as an artificial heart to relieve the organic heart in its task of overcoming an acute process (diphtheria) and as well to replace the lungs temporarily in cases in which a few days will suffice for our modern drugs to overcome infection (for example, in cases of severe pneumonia in the remaining lung after pneumonectomy).

Early experiments in dogs. In preliminary experiments we studied the behavior of the heart and the lung during and after the use of the mechanical device. In these experiments the thorax was widely opened. T cannulas were inserted in both venae cavae and in the aorta. After the venae cavae were clamped near the heart the venous blood was pumped to an oxygenator and from here into the aorta via the side branches of the cannulas.

From these experiments we learned that the electrocardiogram of the heart empty of blood was almost unchanged, and that the heart and the lungs resumed their normal functions immediately when the mechanical device was stopped and the clamps were removed, even when they had been empty of blood (except for the coronary and the bronchial circulation) for more than an hour.

In the second series of experiments we studied methods of applying the artificial heart-lung with as little damage to the animal as possible. The following method was adopted.

From the Physiological Institute of the University of Utrecht.

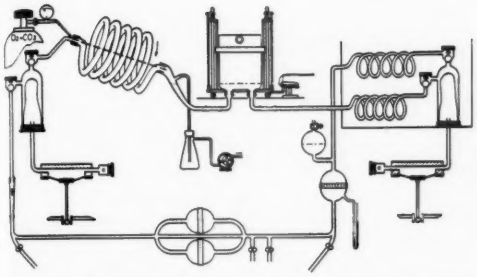

Fig. 1. Schematic diagram of the apparatus. Shunt in use; venous tube coming from the subject (under, left) and arterial tube leading to the subject (under, right) both clamped. In the shunt are 2 filters, a filling and an outlet tube. Further from left to right: rotameter (volume per minute indicator), one venous pump with membrane pump, one spiral oxygenator, assembling tube with bubble aspirator, regulating reservoir, waterbath with one arterial pump, arterial leading with buffer vessel, filter, and pressure meter.

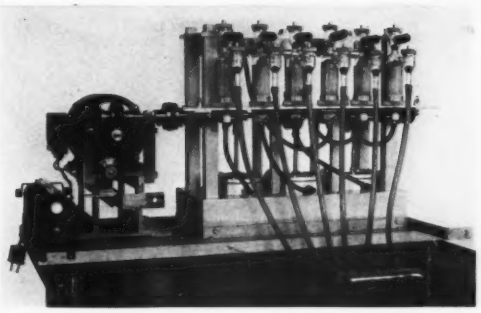

Fig. 2. The 6 venous pumps with their inlet tubes, membrane pumps and motor, which also drives the spiral oxygenators.

A catheter was introduced through the external jugular vein into the vena cava superior close to the heart. A second catheter was brought up high in the vena cava inferior through the femoral vein. Both catheters were connected with a pump (type Dale-Schuster), which sucks the blood from the venae cavae. Careful adjustment of this pump made it possible to aspirate all the blood from the venae cavae just before it enters the heart. The same pump drove the blood to an oxygenator. By a second pump the collected oxygenated blood was forced into the femoral arteries in which T cannulas were inserted. This blood proceeded in the normal direction to the distal parts of the hindlegs and in the abnormal direction in the aorta toward the heart. However, as there was no blood in the left ventricle, the artificial aortic pressure was higher than the pressure in the right ventricle and the aortic valves remained closed. From the aorta the blood flowed normally into the different arterial branches, including the coronary arteries. Thus in performing only the simple operations on the vessels necessary in order to insert the catheters and the cannulas, it proved to be possible to maintain artificial circulation and respiration. If treated aseptically the animal survived without any sign of distress. We have a dog on which the artificial heart-lung system was applied 1 year ago, and the animal behaves still as normal as any dog. This probably is the first dog in the world who has lived an interval of 2 hours without using his own heart and lungs.

Our results were so convincing and the method and apparatus so simple, that I decided to construct a bigger apparatus for future use in man.

General construction of the apparatus. A system of pumps (right heart) sucks the venous blood from the subject and drives it to the oxygenators. The oxygenated blood is collected in a reservoir. A second system of pumps (left heart) forces the oxygenated blood through a heating device back into the subject (see schematic diagram, Fig. 1, from left to right).

The right heart pump system. A modification of the Dale-Schuster pump is used (Fig. 2). The unit consists of 6 single pumps driven by a central 6-fold crankshaft. The movements of the membranes are transported by air to the finger stalls. The glass housings of these finger stalls have inlet and outlet valves, consisting of amber or glass balls in a ground glass fitting. Thus the blood comes in contact only with rubber and glass; there are no metal and no frictionizing parts. The frequency of the pumps can be regulated by changing the speed of the electric motor driving the shaft; the volume per stroke of each pump by a divided tap, which provides a smaller or greater leak in the air-transport system, a method also used by Gibbon. The

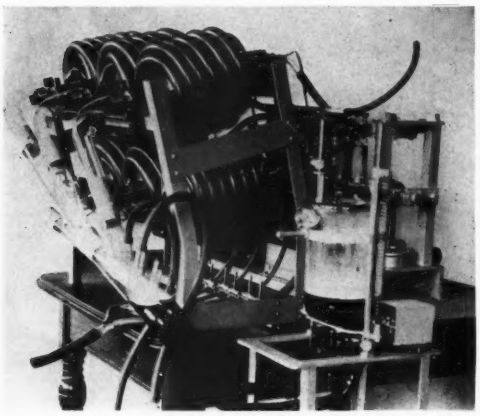

Fig. 3. The 6 oxygenators with the 2 assembling tubes leading to the reservoir. Under left, the main venous tube; on the table, the handles to clamp the 6 venous tubes.

six pumps work alternately, so that constant suction from the caval vein ensues. The volume per minute can be constantly read on a rotameter. At a frequency of 70 per minute, and a volume per stroke of 10 cubic centimeters per pump, the volume per minute is 7 x 6 x 10 cubic centimeters = 4.2 liters. The pumps are mounted on a detachable metal strip and can easily be sterilized together with their tubing.

The spiral oxygenator. As it is practically impossible to insert the organic lungs in an artificial heart circuit, the use of a mechanical heart calls for the use of artificial lungs. Our artificial lung consists of 6 equal parts, one for each right-heart pump (Fig. 3). To avoid the disadvantages of the usual oxygenators we developed a new type of relatively small size and without rapid moving parts, which may cause hemolysis and foaming. Each oxygenator consists of a rigid tube of some suitable plastic material with an internal diameter of 18 millimeters and about 10 meters long. This tube is bent into the shape of a spiral, or to be exact, it forms 3 layers of spirals one in the other, to save space. Both the beginning and end of the tube lie in the central axis of the spiral. The six spirals are mounted in a frame, with their axis pointing slightly downward. They turn about this axis, synchronously with the pumps. Now if a quantity of blood is in the first winding of a spiral it will move all through the spiral and at last come out at the other end. (A similar principle is used by Kolff for diffusion purposes in his artificial kidney (6).) As the blood passes through the spiral tube it will adhere to the wall and form a thin layer. Oxygen (with carbon dioxide) streams constantly through the tube and the blood is readily oxygenated. The volume per stroke of each pump proceeds during one revolution from the first coil of its spiral to the second coil, while simultaneously a new volume of blood is pumped into the first coil and so on. So the stroke volumes of blood pass through the spiral, one after the other, becoming gradually oxygenated.

The oxygen intake in one passage through the spiral on the average is very good; the saturation with oxygen rises for example from 60 to 90 per cent at a volume per minute of 700 cubic centimeters per spiral. This means that with a total minute volume of 6 x 700 c.c. = 4.2 liters, the oxygen intake is 4.2 x 60 c.c. = 252 c.c. per minute, which may be considered sufficient for a man in basal condition.

It is clear that the oxygen-intake will be greater the lower the saturation of the venous

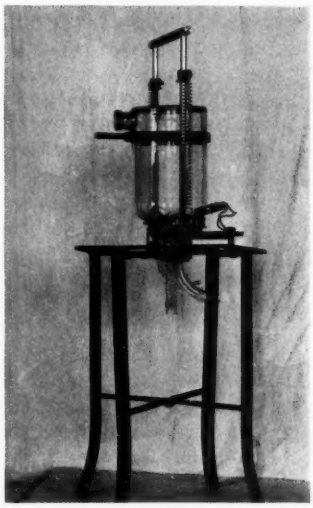

Fig. 4. The regulating reservoir, which prevents air from coming in the arterial system. Two (curved) inlet tubes and one outlet tube.

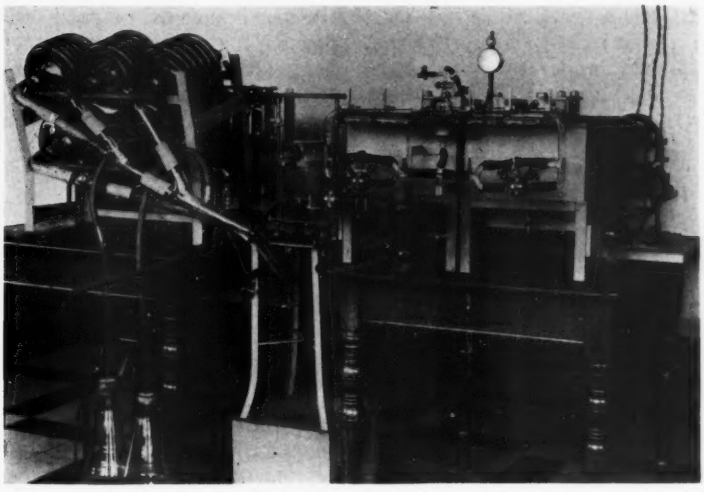

Fig. 5. Overall view of the mechanical heart-lung device. The tables are 80 cm. wide.

blood. With a venous saturation of about 20 per cent we found an oxygen intake of between 90 and 100 cubic centimeters per liter of blood. The accompanying table presents some of our experimental figures in the range from 80 per cent to 50 per cent saturation of the venous blood.

VENOUS SATURATION IN 80 TO 50 PER CENT RANGE

Venous saturation per cent	Arterial saturation per cent	Oxygen intake per liter c. c.
80	96	32
74	94	40
66	90	48
61	88	54
51	85	68

Even after the same quantity of blood had constantly passed the oxygenators for 2 hours and more, we could detect no appreciable hemolysis. There was no foaming in the spirals.

It is our opinion based on our observations that this new type of artificial lung offers much that is promising.

The regulating reservoir. The arterial blood from the oxygenators is collected in a glass reservoir (Fig. 4), from which it is sucked away by the left-heart pumps. To prevent the pumps from sucking air, which would cause air embolism in the subject, they stop automatically when the blood in the reservoir has reached the lowest tolerable level. After about 2 seconds the steady flow from the oxygenators has raised the level and the arterial pumps start their work again. This automatic system to prevent air from coming into the arterial system is very simple: the reservoir hangs in spiral springs and moves by its weight (which depends on the quantity of blood inside), a mercury contact. It is practically not possible to make two sets of pumps which return absolutely the same volume per minute; and even if it were, both the venous return in the subject, as well as the arterial pressure may change a bit from time to time, which would make continuous regulation of the pumps still necessary. It would of course be wrong if the volume per minute of the venous pumps were greater than that of the arterial pumps, because then the blood of the subject would gradually be accumulated in the reservoir. For these reasons the arterial pumps are regulated in such a way that their minute-capacity is just a little greater than that of the venous pumps; then the apparatus functions automatically, the arterial pumps will stop for a few seconds now and then, say once in some minutes, this time interval depending on the degree of exactitude with which the arterial pumps are adjusted.

The left-heart pump system. The left-heart pump (shown at the right in Fig. 5) system consists of 6 pumps similar to those of the right-heart system. They work in two groups of 3 alternately, so that a real pulse results. A pulse seems to be necessary for good perfusion of the organism. The pumps with their inlet and outlet tubes are immersed in a waterbath, kept at such a temperature (about 39°C.) that the outcoming blood registers 37 degrees. The cooling of the blood in the oxygenators is, however, not more than ½ to 1 degree at normal room temperature. The outlet tubes of the pumps join 3 by 3 to a larger tube. Parallel to each of these two tubes runs a tube with a fine filter, so that the blood can be driven at will through or beyond the filters. The two tubes are connected with the two horizontal arms of a cross shaped glass tubing. The upper arm of the cross leads to a buffer-vessel, the upper opening of which is connected with a blood-pressure meter. The tube which leads to the two cannulas in the femoral arteries is connected to the lower arm of the cross. Of course the pressure to be exerted by the arterial pumps depends foremost on the circulatory resistance of the subject. By altering the leak of the membrane pumps it is easy to adjust the blood pumps so that the wanted volume of blood per minute is driven out against the prevalent pressure.

The arteriovenous shunt. From the main arterial tube a shunt tube leads to the suction-side of the venous pumps (Fig. 5). Parallel to this tube we mounted two filter-houses with fine filters. If the tubes leading from and to the subject are closed and the shunt tube is opened, the blood circulates in the apparatus from the venous pumps, through the oxygenators and the reservoir to the arterial pumps in the waterbaths and then through the shunt back to the venous pumps. Thus the apparatus is filled with oxygenated, warm blood before it is applied to the subject. During this shunt-circulation the blood is passed through the filters, so that clots, if there might be any in the blood, are filtered out beforehand. So, when the patient is prepared for operation, that is when the catheters are inserted into the venae cavae superior and inferior (through a jugular and a femoral vein, respectively) and the T cannulas are placed in the two femoral arteries, and when the connecting tubes (after having been filled with blood or saline) are attached to the catheters and the cannulas, one has simply to open the connecting tubes and to close the shunt, and artificial circulation is started.

As circulation is maintained via the shunt, the filters in the main circuit may also be used; during circulation through the subject these filters are of use only in so far as they may withhold clots which originate in the apparatus.

Adjacent apparatus. Each of the tubes leading to the venous pumps and also the inlet and outlet tubes of the arterial pumps are provided with handles so arranged that these tubes can be closed rapidly with one simple movement in case something might go wrong with the relative pump. We have had, however, no trouble whatsoever during the hundreds of hours in which the system has been in use.

As already stated the blood does not foam in the apparatus, but at the blood level, in the assembling tubes, leading from the oxygenators to the reservoir, some bubbles may appear. If they do the bubbles are easily sucked away to a vacuum vessel (Figs. 1 and 5).

The handling of the apparatus. As the apparatus is semiautomatic the handling is very simple and can easily be done by one man. Before use the dead space of the apparatus must be filled with blood (of course in its future use in man it must be filled with blood of the same group as that of the patient) otherwise the blood taken to fill the dead space would lessen the volume of blood of the subject. It takes about 2½ liters of blood to fill the dead space. This may seem like a rather large quantity. Strictly speaking it could be less, as the blood normally present in the lungs (in man about 1 liter) could be taken from the patient. However, as blood, especially human blood, is easily obtainable, I think that the use of 2½ liters will not present a great difficulty. Except for the artificial lungs which hold about 1 liter, the dead space consists of the various tubes, the reservoir, the pumps and the heating system. To

fill the apparatus we use separate inlet and outlet tubes (Figs. 1 and 5). The blood is sucked by the venous pumps into the apparatus directly from the blood-container. The air, or if the system is previously filled with saline, the saline, can escape through the outlet tube. In order not to spoil blood the last quantity of saline can be left in the system to mix with the blood; air bubbles if present can escape via the shunt to the venous part of the apparatus where they mix with the oxygen in the oxygenators and do no harm. When the apparatus is full of blood, the shunt in function, and no air bubbles are present in the arterial part, the apparatus is ready for use. As soon as the connections with the subject are completed and the shunt is closed, the operator adjusts the venous pumps in such a way that a maximum of blood (to read from the rotameter) is sucked from the subject. If suction is too weak only a part of the blood is sucked from the venae cavae. On the other hand if suction is too strong the wall of the veins may be sucked into the openings of the catheters and thus close them. To reduce this difficulty to a minimum we used catheters which have 3 or 4 openings. When optimal suction is established the operator adjusts the arterial pumps, so that the automatic regulator comes into function only now and then. Once this is done the operator has only to give general supervision to the workings of the apparatus, to watch the temperature of the outcoming blood in order to adjust the heat of the waterbath and to keep under control the flow of oxygen (preferably with 5 per cent carbon dioxide). Other than this the apparatus works automatically and reliably; in the hundreds of hours it has been in use we have had not the slightest trouble with it.

Testing the capacity of the apparatus. As the apparatus is meant for use in man, we had to find a way to test its real capacity *in vivo*. For this purpose we used two dogs with a body weight respectively of 30 and 32 kilograms, that is about half the weight of a man. Therefore we used only half of the apparatus, i.e. 3 venous pumps, 3 oxygenators, and 3 arterial pumps. Under these conditions both dogs lived for 2 hours on the mechanical system. The electrocardiograms showed no, or very small, alterations, and when shutting off the apparatus after 2 hours, the organic heart and lungs resumed their functions immediately. To determine whether the mechanical system was sufficient to maintain the life processes, a closed leather mask was tightly fitted over the mouth and nose of the animal, so that it had no chance to breathe. (In our earlier experiments we sometimes clamped the trachea for the same reason.) The animals showed no sign of distress during this procedure and it was obvious that it was just the same whether the mask was present or not. Thus we may take it for granted that oxygenation by the mechanical system was sufficient in these experiments.

Once more I would point to the fact that while in our method the complete circulation is maintained, there is no reason to believe that the functions of the organs (kidney, liver, glands of internal secretion, etc.) are impaired. We may assume therefore that all life processes go on materially unaltered.

In these experiments the volume per minute varied between 1¾ and 2¼ liters; thus if the whole apparatus were used the volume per minute under similar conditions would reach about 4 liters, this indeed being approximately the quantity which is necessary to maintain life in man.

As the experiments proved that half of the apparatus was sufficient to maintain life in dogs of 32 kilograms, we may readily believe that when the whole apparatus is used circulation will be sufficient for a normal man of about 64 kilograms bodyweight.

One might ask whether we know that with our method the heart is really empty of blood. In fact we do not know; it is possible of course that not all the blood is sucked away from the venae cavae, and that part of it still enters the heart cavities. But this would not matter at all. Our experiments just mentioned revealed that enough blood passes through the mechanical system to maintain life, and that is what we want. If the artificial system is used to replace the heart or the lungs to relieve these organs temporarily, it is quite irrelevant if a fraction of the blood passes the organic heart and the lungs; the real test in such cases

is that the mechanical system be sufficient to sustain life. If, on the other hand, the artificial system is used in intracardial operations or the like, then the surgeon may, since the thorax is opened in these cases, clamp the venae cavae close to the heart to be sure that no caval blood enters the heart.

The sterilization of the apparatus. It is necessary of course that it be possible to sterilize the whole system. The 6 venous pumps are mounted on a detachable strip and can, together with their tubing, be put in a sterilizer. The 6 arterial pumps with their tubings can be sterilized by heating to 100 degrees C. in their own water baths. The rest of the glasswork and tubing and the reservoir can also be disconnected and sterilized by heat.

We are, however, looking for a more simple method of sterilization, so that the whole apparatus may be sterilized intact. Therefore experiments are in progress with very promising results. We proceeded as follows. After a general cleansing of the apparatus by perfusing it at its own power with water, a pepsine-HCl solution at 37 degrees circulates through the whole system for about 30 minutes. By this procedure the protein which might adhere to the walls is removed. Then a disinfecting solution circulates through the apparatus for some time, eventually heated to 55 or 60 degrees in the waterbath.

To control sterility, after such a procedure we filled the apparatus with a sterile bouillon solution which circulated for hours in the system. From this bouillon the bacteriologist took samples to test it on different kinds of solutions at various temperatures. In our last experiment he found that from 21 samples 17 were entirely sterile, the other 4 showed a few colonies of nonpathogenic bacteria. He estimates that not more than 1 bacterium per 30 cubic centimeters of bouillon was present. Thus this simple method of autosterilization will surely prove to be effective, as we have stronger disinfectants on our program. To be entirely on the safe side it may seem to be advisable to add penicillin to the blood in the apparatus when in the future the apparatus is used in operations on man.

Special measures. Clotting of the blood must be prevented of course. Until now we did not apply silicon-coating to the apparatus, but, in our experiments on dogs, added an anticoagulant. We used chlorasol-pink or heparin. Both gave good results. Needless to say the necessity to make use of an anticoagulant is a weak point in any extracorporeal circulation procedure. We do not exactly know how a patient will react to a large dose of heparin and in case of extensive operations it is obvious that it may cause difficulties. The only statement I can make is that in our dogs such troubles were far less than we had expected. Especially when used in man we are of the opinion that it will be necessary to use pyrogen-free solutions in the apparatus.

SUMMARY AND CONCLUSIONS

We believe that our apparatus, from a technical standpoint, may be considered ready for a trial in man. For the surgeon there is of course still the question of the use of heparin, and perhaps other unforeseen difficulties of pure medical character may arise. However, in technical and physiological respects we are pretty sure. As to the technical performance, the apparatus did not show any failure during its long hours of use; the capacity of the pumps is such that even if one or two of both the venous or the arterial system might fail, the remaining pumps still have sufficient capacity; and if ever the whole apparatus might stop, nothing serious may occur, since the organic heart takes over its function immediately as soon as the blood is no longer sucked away from the venae cavae. If this should happen exactly at the moment the heart is opened by the surgeon, complications might arise, but this would seem to be a very special coincidence. As to the physiologic aspects, the mechanical heart maintains the whole circulation: to brain, spine, liver, kidney, glands with internal secretion and so on, so that we may expect that all the functions in the organism, nervous, secretory, hormonal, etc., go on more or less normally.

We would not hesitate to use the artificial heart-lung system in a patient in whom other means had failed and there was the possibility of saving his life.

To make the apparatus as reliable as possible our first specimen is heavier and bigger

than really necessary. With the experience gained in the construction of this apparatus we intend to build a second one of smaller overall size.

A description of a mechanical heart-lung apparatus and a method for total artificial circulation are presented. The capacity of the apparatus is sufficient for future use in operations in man.

The artificial lung is based on a quite new principle; the spiral oxygenator causes neither hemolysis nor foaming of the blood.

The possibilities for its application in cases of intracardial operations and the like in man, or as a real artificial heart or artificial lung in cases of serious, acute heart or lung affections are discussed.

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ABNORMAL BLEEDING — II

Further Clinical Experience With Toluidine Blue and Protamine Sulfate

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ABNORMAL bleeding may arise from disorders of the plasma, the formed elements of the blood and the vascular wall. Hemorrhage may occur when any one of these systems is disturbed, although bleeding is frequently complex in origin and may result from disorders which directly or indirectly involve many or all factors concerned with hemostasis. It may be that the vascular factor is affected directly or indirectly in all types of abnormal bleeding.

This report comprises a series of studies carried out on a group of patients with a variety of bleeding disorders. Common to all of the patients of this group was a clotting disturbance revealed by a protamine titration (3).[1] This clotting abnormality was frequently associated with thrombocytopenia, but it also occurred in some patients whose platelet counts were normal. It was absent in others who had severe thrombocytopenia. Also associated with the increased protamine titration in some instances were petechial hemorrhages and positive Rumpel-Leede phenomena, but here again the protamine titration was increased in some patients who had no clinical evidence of vascular change. The clotting time of whole blood was often moderately prolonged; however, this change was detectable only with careful technique. The prothrombin activity was usually normal or near normal. The nature of the clotting defect revealed by the protamine titration remains in question. There are certain similarities between this clotting disturbance and that produced by the injection of commercial beef heparin. However, there are certain distinct differences (1). Resolution of this problem is difficult because many factors are involved, and because the methods of study are inaccurate and not necessarily specific. Present means for heparin identification are not suitable for human use because of the large amounts of blood required to isolate even a few micrograms of crystalline material (7). In addition, the crystalline material may vary considerably in anticoagulant potency (8), and when of poor quality, it may be difficult to identify. The inactivation of the anticoagulant activity of heparin by protamine sulfate or toluidine blue has been frequently interpreted as a biologic means for identifying heparin. Unfortunately, these reactions are shared by other biochemical compounds contained within the body. Some of these are chemically similar to heparin and some are not. Many of these compounds have some anticoagulant activity, although none is as potent as commercial heparin itself. This is further complicated by the fact that most studies have been concerned with beef heparin and that little is known of human heparin.

For these and other reasons the clotting disorder common to these patients and disclosed by the protamine titration can be considered only as resembling that produced by the injection of heparin. Whether the anticoagulant defect is heparin-like in the chemical sense remains to be seen. The term "heparinemia (?)" was used to describe this syndrome in dogs (4). It was used generically to indicate certain similarities between the clotting defect of this syndrome and that produced by heparin in-

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[1]Following the addition of a standard concentration of heparin to normal blood, a remarkably constant amount of protamine is required to restore clotting. (Laboratory normal for males and most females is 0.140 milligram of protamine per milliliter blood containing 0.091 milligram of heparin.

jection. It was interrogated because certain aspects of the problem were and still are unsettled.

METHODS OF STUDY

Coagulation studies included: (1) the protamine titration (3); the normal titration endpoint for humans is 0.140 milligram (protamine requirement) per milliliter of blood containing 0.091 milligram of heparin; (2) whole blood clotting time (1); for normal human blood this is 25 to 35 minutes with the technique used; (3) prothrombin activity—a one stage method with the normal being 100 per cent (10); (4) observation for clot retraction; and, (5) observation for clot lysis 6 and 24 hours after coagulation.

Studies on the formed elements of the blood included erythrocyte, leucocyte, thrombocyte, and leucocyte differential counts and hemoglobin content.

CLINICAL OBSERVATIONS

An analysis of the data obtained on these patients suggests that their hemorrhagic tendency may be advantageously classified with respect to the presence or absence of hemocytologic disorders.

Patients without evident hemocytologic disorders. This group of patients is composed primarily of women, although it has been demonstrated in 2 males who had excessive bleeding after surgical procedures. In women this clotting disturbance has been observed in some cases of menorrhagia (1) and some cases of delayed postpartum hemorrhage. In 2 of the postpartum patients, the hemorrhagic feature was serious; in 1 it was troublesome but less severe (Table I). All 3 showed a prolongation of the whole blood clotting time and an increased protamine titration. The platelet counts and prothrombin times were near normal. A marked increase of fibrinolytic activity was present in 1 patient, Case 2, but this was greatly reduced after the first toluidine blue and protamine administration. The protamine titration, when returned to normal (0.140 mgm.), and maintained there for several days, remained normal. This suggests the self-limiting nature of the disorder in the postpartum group, although toluidine blue may be necessary to hasten the return to normal.

Of interest was the fact that none of these patients had petechiae or a "positive" Rumpel-Leede test, although ecchymoses occurred at the site of needle punctures.

The abstracts of the clinical courses of 2 of these patients are presented below. The menorrhagic group will be reported elsewhere (1).

CASE 1 (Table I). A 32 year old female, secunda gravida, nullipara, was admitted to Chicago Lying-in Hospital, where she delivered after 9 hours of labor. A small cervical laceration was repaired with No. 0 chromic catgut sutures as were the deeper layers of the episiotomy wound. The skin was approximated with four interrupted cotton sutures.

On the ninth postpartum day, uterine bleeding occurred, for which a curettage was done and 600 milliliters of citrated blood were given. Because of the continued bleeding, an incomplete vaginal hysterectomy was performed on the following (10th) day. A 600 milliliter citrated blood transfusion was given. The uterus showed prominent lymphatic channels, no myomas and no retained placenta. Ascorbic acid and vitamin K were given daily thereafter. Bleeding continued from the lower episiotomy wound. This was temporarily controlled by three mattress sutures on the eleventh day, at which time she received 1200 milliliters of citrated blood. No bleeding occurred until the fourteenth day, when spotting was noted along the episiotomy suture line. This was resutured with one mattress suture, which controlled bleeding until the 16th day, when fresh bleeding resumed from the episiotomy site. This area was packed on the 16th day, but oozing continued and the episiotomy was resutured on the 18th day. One 700 milliliters citrated blood transfusion was given on the 16th day and 500 milliliters of blood were given as a direct transfusion on the 17th day.

On the 18th day the protamine requirement in the titration exceeded 0.200 milligram of protamine sulfate and the whole blood clotting time was 47 minutes. The platelet count was 244,000/cubic millimeter and the prothrombin activity was normal. The remaining studies were normal. One milligram of protamine sulfate per kilogram was given intramuscularly every 4 hours for 10 days; bleeding stopped within 4 hours after the initial injection and did not recur. The patient was discharged on the 29th postpartum day. The protamine titration and the clotting time were normal 12 hours after protamine therapy was instituted and remained so even after protamine was discontinued on the 26th day (10th day of protamine sulfate). The blood of the patient was examined 3 months later and found to be normal with reference to the above mentioned clotting studies.

During the hemorrhagic period (9th to 18th postpartum day), the patient received 3,600 milliliters of blood which maintained her

TABLE I.—LABORATORY AND CLINICAL FINDINGS IN A GROUP OF PATIENTS WITH POSTPARTUM BLEEDING AND AN INCREASED PROTAMINE TITRATION

Patient	Age	Diagnosis	Protamine titration in mgm.		Laboratory data clotting time in min.		Prothrombin time %	Platelets	Therapy	Manifestations of bleeding	Clinical response and time of response
			Before therapy	After therapy	Before therapy	After therapy					
385329 (Case 1)	32	Postpartum hemorrhage	>0.20	0.14	47	18	100	244,000	3.0 mgm./kgm. Protamine Daily × 10	Uncontrolled vaginal bleeding which did not respond to numerous resuturing attempts, blood transfusions, or hysterectomy	Complete cessation of bleeding within 4 hours. No further bleeding. Recheck at 3 mo. showed all coagulation studies normal
418980 (Case 2)	25	Postpartum hemorrhage	0.40	0.20 (2 hr.)	120	30	54	260,000	6.0 mgm./kgm. toluidine blue 3.0 mgm./kgm. protamine	Postpartum hemorrhage and blood transfusion reaction—profuse bleeding, which slowed after perineal repair and vaginal pack. Marked fibrinolysins	Clotting time and protamine titration were decreased within 2 hours. A slight oozing around pack continued
			0.20	0.14	30	30	64		6.0 mgm./kgm. toluidine blue Daily × 2 3.0 mgm./kgm. protamine Daily × 6	Continued slight oozing around pack	Clinical and laboratory response immediate. No further bleeding
451162 (Case 3)	26	Postpartum hemorrhage	0.16	0.14	25	18	80	180,000	6.0 mgm./kgm. toluidine blue 3.0 mgm./kgm. protamine	Irregular postpartum bleeding of 26 days which did not respond to dilatation and curettage. Vaginal pack was required. Oozing continued around pack	Oozing around pack slowed and stopped within a few hours
									6.0 mgm./kgm. toluidine blue Daily × 5 3.0 mgm./kgm. protamine Daily × 4	Pack removed with minimal bleeding	No further bleeding

erythrocyte count at 3,080,000 and her hemoglobin at 10 grams per cent. A slight febrile reaction followed the two transfusions given on the 11th postpartum day.

CASE 2 (Table I). Report of this case has been presented elsewhere (1).

CASE 3 (Table I). A 26 year old female, was delivered at the Chicago Lying-in Hospital. Bleeding was slightly in excess of normal immediately after delivery but required no transfusion. The placenta was intact. No abnormal bleeding occurred after 2 hours and the remainder of the postpartum course was uneventful. She was discharged on the 9th day on 0.0002 gram of ergotrate because of subinvolution of the uterus.

She was readmitted on the 18th postpartum day because of vaginal bleeding of 4 days' duration. On bed rest this subsided in 3 days and she was again discharged.

Two days later she was readmitted because of recurrent bleeding. On this day a dilatation and curettage were performed; bleeding was excessive and the uterus was packed, but some bleeding continued through the pack for 36 hours and hysterectomy was contemplated. At this time (36 hours after packing), the whole blood clotting time was normal (25 minutes), but the protamine titration was increased to 0.160 milligram. The platelet count was 180,000 and the prothrombin activity was normal. There was no evidence of excessive fibrinolysin. She was given 6 milligrams of toluidine blue per kilogram and 3 milligrams of protamine sulfate per kilogram intravenously. Two and one-half hours after administration the protamine titration was normal, as was the clotting time. At this time the uterine pack was removed and no bleeding occurred. Four milligrams of toluidine blue per kilogram was given 6 hours later. Six milligrams of toluidine blue per kilogram was administered daily after removal of the pack for 5 days and 1 milligram per kilogram protamine sulfate was given intramuscularly every 6 hours for 4 days. No further bleeding occurred. The protamine titration remained normal after the initial toluidine blue injection. She was discharged on the

9th hospital day and the 29th postpartum day. Follow-up studies have been normal to date (4 months).

Patients with hemocytologic disorders. The primary diseases in the patients comprising this group were varied, but all showed severe marrow disturbances resulting from their primary disease or therapy. The protamine titrations in most cases were increased as were the whole blood clotting times. In addition, and in contradistinction to those patients presented above, most of these patients had thrombocytopenia; many had petechiae as well as ecchymoses. The bleeding tendencies in these patients were complicated in that platelet and vascular disorders existed in addition to the increased protamine titration. In this group all three of these factors contributed to the hemorrhage. The return to normal of the titration when toluidine blue was administered lessened the patients' hemorrhagic tendency only to the extent that the factors responsible for the abnormal titration contributed to bleeding. In no case was the platelet count appreciably altered by this therapy and, so far as clinical tests show, the vascular abnormality was not improved. Hence, this antihemorrhagic therapy was incomplete in that the vascular and platelet disorders remained unchanged.

Representative case abstracts of five patients are presented below:

CASE 4 (Table II). A 7 year old male, entered the Bobs Roberts Hospital with a diagnosis of acute stem cell leucemia. Aminopterin therapy was started as a 1 milligram daily dose for 3 days. During the second 3 days the dosage was increased to 2 milligrams per day and reduced to 1 milligram on the 7th day when petechiae appeared. On the 7th and 8th days there were large ecchymoses. On the 8th day hematemesis occurred and blood was present in the stool. Aminopterin was discontinued after the seventh day.

At this time the protamine titration was 0.180 milligram, the whole blood clotting time was 45 minutes, the platelet count was 24,000 and the prothrombin activity was 100 per cent of normal. Toluidine blue, 8 milligrams per kilogram, was given intravenously on the 8th and 9th days. This was augmented by a 1 milligram per kilogram dose of intramuscular protamine twice daily during the same period. All evidence of bleeding ceased after 48 hours and no new petechiae or ecchymoses formed. Except for a 24,000 platelet count, all other clotting studies were normal 24 hours after the first injection of toluidine blue. Eight days later the first signs of remission of the leucemic process appeared, improvement continued, and temporary remission was obtained. Clotting studies were normal and there was no bleeding in the period of remission.

CASE 5 (Table II). A 38 year old white housewife, has been observed frequently in Billings Hospital for 8 years because of abnormal bleeding. As a very young child, she bled excessively and bruised so easily that there was a family interdictment against spanking. Menstruation from its beginning at 16 years of age was so excessive and prolonged that she became acclimatized to a constant state of profound anemia; her red blood count remained in the neighborhood of 2,500,000 per cubic millimeter and the hemoglobin around 5 grams per cent. The platelet count remained between 125,000 and 250,000 per cubic millimeter on numerous occasions until 1944, when more definite evidence of thrombocytopenia developed. She finally consented to x-ray sterilization, which was carried out March 24 and 25, 1944; a depth dose of 400 roentgens was given to each ovary. Vaginal bleeding, epistaxis and oral bleeding continued, and the platelet count fell and varied between 25,000 and 100,000. Because of this x-radiation of the spleen (total 800 r) was given over a 10 day period in late July, 1944. The platelet count was not appreciably affected; splenectomy was advised but refused. Whether related to x-ray therapy or not, the bleeding materially lessened; the red blood count and hemoglobin returned to normal levels; and the patient complained of plethora (dizziness, feeling of fullness in head, and warmth). The plethora disappeared in 1946 when severe menses resumed, although purpuric manifestations did not reappear until 6 months later, January, 1947. These bleeding manifestations continued; the period of menstrual flow increased from 10 days to 41 days.

Of interest was the fact that the Rumpel-Leede test was always strongly positive, but spontaneous petechiae were absent. Ecchymoses were the only obvious manifestations of her cutaneous bleeding.

Her most recent hospital admission was after 40 days of vaginal bleeding. At this time the hemoglobin was 8.0 grams per cent; the red cell count was 2,400,000; the platelet count was 40,000; the bleeding time as always was prolonged to over 20 minutes. The clotting times throughout the 8 year study were normal.

The protamine titration was first performed on this patient June 22, 1948, at which time her bleeding state was active. The titration was increased to 0.180 milligram of protamine. Seven milligrams of toluidine blue per kilogram of body weight was given intravenously; 6 hours later the titration was normal; at the end of 24 hours, bleeding had stopped. Three blood transfusions, each 500 milliliters, were given over the next 3 days (June 23 to 25). Vaginal bleeding resumed June 28, at which time the protamine titration was again increased 0.040 milligram above normal. On June 29, 7 milligrams of toluidine blue per kilogram of body weight were again given and

TABLE II.—SUMMARY OF LABORATORY AND CLINICAL DATA OF BLEEDING PATIENTS WITH AN INCREASED PROTAMINE TITRATION

Patient	Age and sex	Diagnosis	Laboratory data						Therapy	Manifestations of bleeding	Clinical response and time of response
			Protamine titration in mgm.		Clotting time in min.		Prothrombin time %	Platelets per cu.mm.			
			Before therapy	After therapy	Before therapy	After therapy					
Group A. Acute Leucemia											
456363 (Case 4)	7—M	Stem cell leucemia with aminopterin Rx	0.18	0.16	27 45	12	100	140,000 24,000	8.0 mgm./kgm. toluidine blue Daily × 3	Oral bleeding, large subcutaneous hematomas and petechiae	Oral bleeding stopped no further subcutaneous bleeding. 24 hours.
438819	26—M	Myelogenous leucemia	0.18	0.14	13	32	60	225,000	4.5 mgm./kgm. toluidine blue Daily × 4	Diarrhea with fresh blood and tarry stools. Bleeding from sternal puncture site 3 days before had required sand bag pressure to control	Within 24 hours there were normal colored stools, but 4 benzidine. within 48 hours stools were blood free
439803	5—M	Stem cell leucemia with aminopterin Rx	0.18	0.14	27	33	100	44,000	2.0 mgm./kgm. toluidine blue Daily × 3	Hematomas at injection sites	No further bleeding at sites of needle trauma. 48 hours
453730	3—F	Stem cell leucemia with aminopterin Rx	0.18	0.14	45	18	100	190,000 17,000	3.0 mgm./kgm. Protamine every 6 hrs Daily × 4	Gingival bleeding and ulcerations	Slow clearing of ulcerations and bleeding. 48 hours
M.K.	24—F	Monocytic leucemia with aminopterin Rx	0.18	0.16	23	20	65	20,000	4.5 mgm./kgm. toluidine blue Daily × 4 every other day thereafter	Oral, nasal, and rectal bleeding. Numerous fresh petechiae and ecchymoses	Oral and nasal bleeding stopped within 24 hours. Rectal bleeding stopped within 48 hours. No new ecchymoses and fewer petechiae. Only further bleeding was with trauma to nose. 48 hours
413730	25—F	Lymphatic leucemia	0.18	0.16	35	20	75	52,000	4.5 mgm./kgm. toluidine blue Daily × 2	Oral bleeding, moderate continuous vaginal bleeding	Oral bleeding stopped Some slowing of vaginal bleeding. 24 hours
Group B. Chronic Leucemia											
310214	54—M	Chronic myelogenous leucemia	0.18	0.16	56	30	80	172,000 135,000	4.5 mgm./kgm. toluidine blue Daily × 6 2.5 mgm./kgm. protamine irregularly	Marked gum bleeding	Bleeding slowed in 6 hours. Stopped in 3 days
451925	45—F	Chronic myelogenous leucemia	0.16	0.14	45	31	80	300,000	4.5 mgm./kgm. toluidine blue and protamine	Bleeding from tooth sockets post extraction. Marked fibrinolysis	Required 1800 ml. of whole blood. Bleeding slowed in about 6 hrs. Stopped in 24 hours
Group C. Irradiation											
423054	40—F	Cancer of breast radiophosphorous (P^{32}) therapy	0.18	0.16	30	—	100	100,000	6.0 mgm./kgm. toluidine blue every 2 days × 6	Oral bleeding and leg petechiae	Oral bleeding stopped no fresh petechiae 6 hours
J.M.	65—M	Chronic leucemia 150r spray	0.18	0.16	30	15	90	10,000	4.5 mgm./kgm. toluidine blue Daily × 5	Bleeding from nose, nasal pharynx and razor cut on chin. (transfusions—no effect)	Bleeding less in 12 hr. Slowly ceased in 36 hr. No transfusions during this period
417462	45—F	Cancer of thyroid radioiodine(I^{131}) therapy	0.16	0.14	20	20	100	—	6.0 mgm./kgm. toluidine blue irregularly	Gross hematuria 7 wks. following last isotope treatment. Recurrence in 2 wks.	Initial hematuria stopped 12 hours after toluidine blue injection. Second episode stopped in 24 hours

TABLE II.—SUMMARY OF LABORATORY AND CLINICAL DATA OF BLEEDING PATIENTS WITH AN INCREASED PROTAMINE TITRATION—CONTINUED

Patient	Age and sex	Diagnosis	Laboratory Data: Protamine titration in mgm. Before therapy	Protamine titration in mgm. After therapy	Clotting time in min. Before therapy	Clotting time in min. After therapy	Prothrombin time %	Platelets per cu.mm.	Therapy	Manifestations of bleeding	Clinical response and time of response
Group D. Hodgkin's Disease with Nitrogen Mustard Therapy											
341183	44—F	Hodgkin's disease	0.20	0.16	—	—	—	124,000	3.0 mgm./kgm. protamine	Oral bleeding and bleeding from sternal puncture wound. (No response to local hemastasis or transfusions)	Bleeding ceased and titration returned toward normal in 3 hours
395060	28—F	Hodgkin's disease	0.20	0.14	52	60	60	83,000 68,000	6.0 mgm./kgm. toluidine blue Daily × 2	Oral bleeding and massive subcutaneous hematomas	Oral bleeding stopped in 12 hours
409460	37—F	Hodgkin's disease	0.20	0.14	37	27	95	64,000	6.0 mgm./kgm. toluidine blue Daily × 5	Oral and gingival bleeding with ulcerations. Rectal bleeding. Many petechiae	Oral bleeding ceased within 24 hours. Rectal bleeding stopped in 48 hours
435361	58—F	Hodgkin's disease	0.16	0.14	38	23	77	75,000	6.0 mgm./kgm. toluidine blue	Oral bleeding. Bloody and tarry stools	Oral bleeding slowed and stopped in 48 hrs.
453179	62—F	Hodgkin's disease	0.16	0.14	105	34	85	19,000	6.0 mgm./kgm. toluidine blue Daily × 8 6.0 mgm./kgm. protamine 4.5 mgm./kgm. protamine irreg. thereafter	Aplastic marrow bleeding from sternal puncture wound. Urinary tract bleeding	Sternal marrow bleeding stopped in 30 hrs. Hematuria started 2nd day and decreased on 5th day. Titration returned to normal. Microscopic hematuria lasted to the 8th day
Group E. Thrombocytopenia											
M.S.	30—F	Idiopathic thrombocytopenia purpura (Werlhof's disease)	0.18	0.14	—	—	—	93,000	4.5 mgm./kgm. toluidine blue 4.5 mgm./kgm. protamine Daily × 5 every other day to day 10	Vaginal bleeding and nasal bleeding (pregnant)	Within 72 hours, the vaginal bleeding slowed and epistaxis stopped. Vaginal bleeding slowly lessened until splenectomy on day 10. (Aborted postoperatively)
D.T.	56—M	Toxic pancytopenia	0.18	0.14	42	29	86	16,000	3.0 mgm./kgm. toluidine blue Daily × 7	Oral bleeding. Gross hematuria	Oral bleeding slowed and stopped in 3 days. Hematuria stopped in 10 days. Titration returned to normal
235457 (Case 5)	39—F	Atypical thrombocytopenia purpura	0.18	0.14	15	15	100	60,000	7.0 mgm./kgm. toluidine blue	Vaginal bleeding of 30 days. Petechiae and ecchymosis	After 6 hours the vaginal bleeding stopped. No new ecchymosis. There was no effect on the petechiae
			0.20	0.14	15	15	100	—	7.0 mgm./kgm. toluidine blue Daily × 3	Vaginal bleeding resumed 2 days after discontinuance of toluidine blue	Bleeding stopped within 12 hours. Further remissions after stopping therapy were controlled
15517 (Case 7)	26—F	Secondary thrombocytopenia purpura	0.18	0.18			100	110,000	6.0 mgm./kgm. toluidine blue 4.5mgm./kgm. protamine	Vaginal bleeding of 20 days. Easy bruising	Spotting after protamine. Stopped within 14 hours after toluidine blue
			0.18	0.14	—	—	—	85,000	6.0 mgm./kgm. toluidine blue	No bleeding	Titration returned to normal
			0.18	0.14	50	32	—	15,000	4.5 mgm./kgm. protamine	Recurrent vaginal bleeding	Stopped within 7 hours
			0.18	—	53	—	100	—	6.0 mgm./kgm. toluidine blue	Vaginal bleeding. Signs of intracranial bleeding	Died of intracranial hemorrhage. Had received no therapy for 2 days preceding terminal stage

followed by one whole blood transfusion. Bleeding again stopped. The same toluidine blue dose was again given June 30 and July 1. The protamine titration promptly returned to normal until July 4, when it was increased to 0.200 milligram July 5, with bleeding continuing, 7 milligrams of toluidine blue per kilogram of body weight and 500 cubic centimeters of blood were given, and bleeding stopped. Splenectomy was performed on July 6. The immediate preoperative protamine titration was normal; 4 hours after operation it increased to 0.180 milligram and 7 milligrams of toluidine blue per kilogram of body weight were given later in the day. The following day the titration was decreased to 0.160 milligram but, because the platelet count was normal (340,000), no more dye was given. The titration returned to normal on July 9, the third postoperative day. Abnormal bleeding did not recur; the Rumpel-Leede test returned to normal; the bleeding time was 3 minutes. These tests, including the protamine titration, have continued normal to date (7 months).

The diagnosis of idiopathic thrombocytopenic purpura in this patient was based upon thrombocytopenia and marrow studies in which no platelets were seen in spite of numerous megakaryocytes. The fact that the history of bleeding antedated the thrombocytopenia by so many years raises the question as to the basic disturbance. An agnogenic clotting defect was described in this patient 8 years ago (5). This was demonstrated on recalcification of plasma and the addition of extreme dilutions of thromboplastin. It may be that the original plasma clotting defect and the thrombocytopenia which developed later were independent phenomena or that there were a cause and effect relationship not otherwise understood.

CASE 6 (Table IV). This patient suffered from idiopathic thrombocytopenic purpura without any increase in the protamine titration and did not respond to toluidine blue therapy. This patient was a 28 year old male who was admitted to Billings Hospital. He was troubled with epistaxis and cutaneous petechial hemorrhages most marked over the legs. The spleen was not palpable. Laboratory findings showed no anemia but thrombocytopenia was present, varying from 35,000 to 100,000 platelets per cubic millimeter. The leucocyte count was 8,500; the differential count was normal. The bleeding time was moderately prolonged up to 24 minutes but the whole blood clotting time was normal. The protamine titrations were normal on 5 occasions. The sternal marrow disclosed no free platelets, although the megakaryocytes were normal in number. The diagnosis of Werlhof's disease was made.

The patient was given toluidine blue on 4 occasions with no effect on petechiae formation as measured by the Rumpel-Leede test before and 12 hours after dye administration. Splenectomy was performed and the platelet count responded rapidly, reaching 200,000 within 24 hours. The Rumpel-Leede test was negative when tested 4 days after splenectomy. One week after operation the sternal marrow contained large numbers of platelets in and around the megakaryocytes (normal). The patient is asymptomatic with a normal platelet count 5 months after splenectomy.

CASE 7 (Table II). A 28 year old white female, was admitted to Billings Hospital September 30, 1948, with the chief complaints of easy bruising and intermittent vaginal bleeding for 5 weeks.

She stated that she had been well until August, 1948, when she noted the spontaneous appearance of small red spots and bruises on her skin. Her menstrual period at this time was exceptionally heavy. The flow continued and she was admitted to another hospital September 10. There she received six blood transfusions with no effect on her bleeding. Her protamine titration at this time was increased to 0.180 milligram of protamine. She was given 4.5 milligrams per kilogram of body weight of protamine sulfate and 24 hours later she was only spotting. She was then given 6 milligrams per kilogram of body weight of toluidine blue and the vaginal bleeding stopped. The protamine titration returned to normal. Clotting times were not done at this time. She continued to show petechiae. The stools remained positive for blood. On September 21, 5 days after discontinuing toluidine blue therapy, she began bleeding vaginally and continued until admitted to Billings Hospital on September 30. Numerous hemorrhages were present in the eye grounds and in the mucous membranes of the mouth. There was no nasal or oral bleeding.

The urine contained many red blood cells. The erythrocyte count was 2,020,000 per cubic millimeter. The hemoglobin was 8.5 grams per cent. The leucocyte count was 1,900 per cubic millimeter. The differential leucocyte count showed 76 per cent small lymphocytes and 18 per cent neutrophils. Normoblasts were present in the peripheral blood. The thrombocyte count was 15,000 per cubic millimeter. Prothrombin activity was normal, the protamine titration was 0.180 milligram and the whole blood clotting time was 50 minutes. The bone marrow showed absence of platelets and megakaryocytes.

On the evening of admission she was given 4.5 milligrams per kilogram body weight of protamine sulfate intravenously. The vaginal flow stopped within 12 hours and the protamine titration returned to normal. A single daily dose of 2.5 milligrams per kilogram of protamine sulfate was given for 5 days. The bleeding was controlled and the clotting studies remained normal until the fifth day when the titration suddenly increased to 0.180 milligram and the clotting time increased to 53 minutes. On the sixth day vaginal bleeding resumed and new ecchymoses

appeared. She refused toluidine blue because of nausea. The following day (7th hospital day), she complained of severe headache and nuchal rigidity was demonstrated. She became comatose several hours later; and, despite whole blood transfusions, protamine sulfate, toluidine blue, and hypertonic glucose, she became progressively worse and died 18 hours later.

At autopsy massive intracranial hemorrhage, hemorrhagic gastroenteritis, and about 100 milliliters of free blood in the peritoneal cavity (probably from a ruptured hemorrhagic ovarian cyst) were found.

Blood drawn at the time of death showed a complete absence of fibrinogen. The patient's blood lysed normal blood clots in dilution of 1 part patient's blood to 9 parts normal blood.

CASE 8 (Table III). A 38 year old white female, had carcinoma of the breast with metastases to the ribs, spine, and pelvis. During a period of 4 months, she received repeated heavy doses of x-ray (an original 5000 r and then 2400 r to each of four involved bony areas). One month after the last dose, bleeding occurred about the mouth, especially from the lips and the tongue. There were large submucosal hematomas which threatened occlusion of the respiratory and alimentary tracts. At this time the platelet count was 10,000 per cubic millimeters and the leucocyte count was 800. Numerous blood transfusions, vitamin K, vitamin C and rutin failed to check the bleeding.

Toluidine blue (6.0 mgm. per kgm.) was given daily for 5 days. Bleeding stopped a few hours after the first injection and the hematomas began to organize. Five days after discontinuing therapy bleeding returned. She was then given on alternate days 6.0 milligrams per kilogram of toluidine blue and 6.0 milligrams per kilogram of protamine sulfate for 2 weeks. The bleeding stopped and sloughs disappeared. No further bleeding occurred to the time of her death 6 weeks later from carcinomatosis.

Table III lists a group of bleeding patients with a clinical response to toluidine blue and protamine sulfate. Laboratory data were incomplete or obtained early in the study and were not suitable for comparative purposes.

Table IV lists a group of bleeding patients with little or no clinical response. Many of these patients demonstrate the failure of therapy when the titration was normal. Some of these received inadequate therapy by present standards. Patient B.R.I. is notable as a complete failure on routine therapy; however, the abnormal protamine titration was likewise unaffected. This failure was not understood and based on the studies of other patients, some response was expected.

Table V presents clotting studies and platelet counts on a group of patients with a variety of disorders. The lack of association of thrombocytopenia with the protamine titration is again demonstrated. Of 11 patients with idiopathic thrombocytopenic purpura, 6 had normal protamine titrations. One patient, Case 5, with an abnormal titration, had fairly good though incomplete clinical response to toluidine blue and protamine. Four bleeding patients with normal protamine titrations had no response to therapy. Three other bleeding patients had some clinical response to therapy, but in none was the response sufficient to warrant withholding splenectomy.

Clotting factor deficiencies, as in hemophilia and prothrombin deficiency (dicumarol therapy) produce abnormalities in the titration only in so far as they prevent clot formation, the end-point. These disorders can be recognized with other tests, and they do not respond to toluidine blue and protamine therapy.

TOLUIDINE BLUE AND PROTAMINE SULFATE ADMINISTRATION

The factors responsible for the increased protamine titration and prolonged clotting time persist for varying periods of time. Successful therapy should afford adequate and continuous control of these factors as long as they contribute to bleeding. In most instances the resultant defects appear to be temporarily controlled by adequate toluidine blue for 12 to 36 hours. The action of protamine sulfate was much shorter, probably less than 2 hours, and was less efficient than toluidine blue in patients whose hemorrhagic disease was complicated by other blood disorders. In the profusely bleeding patient the simultaneous administration of protamine sulfate with toluidine blue was used to take advantage of the faster initial action of protamine.

The amount of toluidine blue required to control bleeding and to restore the protamine titration to normal varied considerably in different patients. The extent to which the protamine titration was increased did not prove indicative of the toluidine blue requirement. However, a return to normal of the titration paralleled clinical improvement from the standpoint of hemorrhage in most patients.

The following therapeutic regimen is currently employed. During the first 3 days, a

TABLE III.—THERAPEUTIC AND CLINICAL DATA ON A FURTHER GROUP OF PATIENTS

Patient	Age and sex	Diagnosis	Therapy	Manifestations of bleeding	Clinical response
L.A.U.	2¼—F	Acute monocytic leucemia	3.0 mgm./kgm. toluidine blue 2.0 mgm./kgm. toluidine blue Daily × 7	Oral, lip, gum, and cheek bleeding which did not respond to blood transfusions, vitamins C and K, or rutin. Skin petechiae	Bleeding about the mouth stopped within a few hours. No new petechiae. Repair of ulcerations took 10 days
L.U.S.	49—F	Acute myelogenous leucemia	1.0 to 3.0 mgm./kgm. (varying dosage) toluidine blue Daily × 4	Oral bleeding, making basin under chin necessary. Did not respond to blood transfusions, vitamins C and K, rutin, or calcium gluconate	Bleeding cleared within 1 to 3 hours after 3.0 mgm./kgm. of toluidine blue. Lower doses allowed recurrences which immediately responded to the 3.0 mgm./kgm. dose
I.P.D.	5—F	Acute stem cell leucemia	2.5 mgm./kgm. toluidine blue Daily × 2	Bleeding from mouth, nose, and eyes. Hematuria	Diminution of bleeding from eyes, nose, and mouth. No effect on hematuria. Note low dose and short period of therapy.
A.L.R.	23—M	Acute lymphatic leucemia	6.0 mgm./kgm. toluidine blue	Severe oral bleeding	Bleeding stopped 3 hours after single dose of toluidine blue. Pt. died in 2 days; autopsy showed no hemorrhage
M.S. Case 8	38—F	Metastatic breast carcinoma. Irradiation: 5000 r } to skull, ribs, 2400 r } pelvis, and lumbar spine	6.0 mgm./kgm. toluidine blue Daily × 5 No therapy—5 days 6.0 mgm./kgm. toluidine blue and protamine, alternate days × 5	Bleeding from gums, cheeks, and tongue with massive submucosal hemorrhages treatening to close off respiratory and alimentary tracts. Bleeding of gums and cheeks recurred after 5 days of no therapy	Bleeding controlled within 2 days and ulcerations cleared within 4 days of initial therapy. Bleeding cleared within 2 days of second period of therapy
P.E.R.	27—F	Chronic pyelonephritis and uremia	6.0 mgm./kgm. toluidine blue	Vaginal bleeding and pressure cuff on arm produced petechiae	Vaginal bleeding stopped within 12 hours. Pressure cuff negative. No further bleeding.
J.A.R.	34—M	Chronic glomerulonephritis and uremia	4.5 mgm./kgm. toluidine blue	Severe nasal bleeding	Nasal bleeding stopped within 24 hours. Single dose of dye. Excretion was slow
C.H.R.	41—F	Idiopathic thrombocytopenia purpura (Werlhof's disease)	2.5 mgm./kgm. toluidine blue every other day × 6 Single dose 1 wk. later	Oral bleeding of 8 months' duration. Many petechiae over extremities. Recurrence while off therapy. Refused treatment, died of intracranial hemorrhage	Oral bleeding stopped after each period of therapy. No new petechiae appeared
H.O.L.	10—F	Idiopathic thrombocytopenia purpura (Werlhof's disease)	3.0 mgm./kgm. toluidine blue Daily × 4	Spontaneous petechiae. Bleeding from gums	Gum bleeding stopped and spontaneous petechiae decreased
O.A.K.	22—F	Idiopathic thrombocytopenia purpura (Werlhof's disease)	2.0 mgm./kgm. toluidine blue irregularly	(Postsplenectomy) Showers of petechiae. No change with transfusions. Menorrhagia requiring hysterectomy	At various intervals there was suppression of petechiae formation after toluidine blue therapy in the presence of a decreasing platelet count. This low dosage failed to alter menstrual flow

daily intravenous dose of toluidine blue of 7 to 10 milligrams per kilogram of body weight is given regardless of the clinical response. If bleeding is not controlled, this dosage is continued for a total of 6 days. If after the third day the titration has returned to normal, the dosage is cut in half and this reduced dose is given daily on the fourth, fifth, and sixth days. Thereafter, it is administered when the protamine titration increases. This dosage schedule is followed in both children and adults.

Toluidine blue was prepared from the powder as a 1 gram per cent aqueous solution and was sterilized by Seitz filtration. This procedure served not only to sterilize but also to remove particulate matter. It was not autoclaved. The amount required for each patient was pipetted into 500 milliliters of normal saline and was administered intravenously over a period of 2 to 3 hours.

Protamine sulfate was administered intravenously in 200 to 300 milliliters of normal saline over a period of not less than 40 minutes, because some anaphylactoid reaction may occur with rapid administration.

Reaction to toluidine blue thus far has been limited to brief periods of nausea and vomiting in about 15 per cent of our patients. Patients who developed these symptoms on one occasion frequently failed to have them on subsequent doses and vice versa. Protamine sulfate produced occasional headache and flushing.

TABLE IV.—SUMMARY OF LABORATORY AND CLINICAL DATA ON BLEEDING PATIENTS WITH LITTLE OR NO RESPONSE TO TOLUIDINE BLUE AND/OR PROTAMINE SULFATE THERAPY

Patient	Age and sex	Diagnosis	Laboratory data						Therapy	Manifestations of bleeding	Clinical response and time of response
			Protamine titration in mgm.		Clotting time in min.		Prothrombin time %	Platelets per cu.mm.			
			Before therapy	After therapy	Before therapy	After therapy					
S.U.T. (Case 6)	28–M	Idiopathic thrombocytopenia purpura (Werlhof's disease)	0.14	0.14	28	31	90	40,000	6.0 mgm./kgm. toluidine blue × 4 irreg.	Showers of petechiae	No effect
H.A.N.	13–F	Idiopathic thrombocytopenia purpura (Werlhof's disease)	0.14	0.14	—	—	100	3,000	3.0 mgm./kgm. toluidine blue	Numerous petechiae, Vaginal bleeding	No effect. Spenectomy performed—bleeding stopped
M.O.R.	26–F	Idiopathic thrombocytopenia purpura (Werlhof's disease)	0.14	0.14	18	18	100	168,000	1 mgm./kgm. toluidine blue 2 times wkly. for period of 2 mo.	Showers of petechiae. Vaginal bleeding	Petechiae were controlled during dye therapy, but would recur. Vaginal bleeding controlled only one time
Y.O.U.	28–F	Idiopathic thrombocytopenia purpura (Werlhof's disease)	0.14	—	42	—	72	66,000	4.5 mgm./kgm. protamine	Many petechiae. Vaginal bleeding 5000 ml. Blood had no effect.	No effect from protamine. Splenectomy done
S.K.Y.	30—F	Thrombocytopenia purpura	0.14	0.14	19	15	100	60,000	3.0 mgm./kgm. toluidine blue	Purpura, oral bleeding and ulceration; vaginal bleeding	No effect
S.P.E.	8—M	Hemophilia	0.20	0,20	—	—	—	—	3.0 mgm./kgm. protamine	Hematoma in neck and under tongue	No effect, no change in titration
R.P.B.	51—M	Chronic myelogenous leucemia	—	—	17	17	80	2,000	1 mgm./kgm. toluidine blue	Mild gum bleeding for 1 mo., severe for 7 days	No effect from single small dose
P.E.T.	26—F	Mycosis fungoides	0.20	0.20	—	—	—	78,000	3.0 mgm./kgm. toluidine blue	Oral bleeding. Bleeding from needle puncture sites. Subcutaneous hematomas	No effect from single small dose
W.I.L.	48—F	Aplastic anemia	Prolonged clotting and bleeding times					20,000	0.5 to 1.5 mgm./kgm. toluidine blue irregularly	Oral bleeding	Complete, but temporary, control of bleeding after each administration of dye. Short period and low dosage
B.R.I.	40—M	Lymphoma	0.18	0.18	42	60	80	26,000	6.0 mgm./kgm. toluidine blue	Severe nasal bleeding unaffected by transfusions. Hematuria	No effect on the bleeding. Titration unaffected
			0.18	0.18	25	39	75	28,000	6.0 mgm./kgm. toluidine blue	Hematuria-losing 100 to 200 c.c. of blood every 3 hours. Irregular nasal bleeding	No effect. Titration unaffected

Intramuscular protamine produced some local pain, similar to that seen on intramuscular administration of free penicillin.

These doses do not relate to the therapeutic control of hermorrhage from overheparinization. Current studies indicate that other substances which are more physiologic than toluidine blue may be equally effective, such as gelatin (1).

DISCUSSION

In connection with the data herein presented, the work of Astrup and Volkert (11,

TABLE V.—CLOTTING STUDIES AND PLATELET COUNTS IN VARIOUS PATHOLOGIC STATES

Patient	Diagnosis	Protamine titration in mgm.	Clotting time in minutes	Prothrombin time—%	Platelets
E.V.	Werlhof's	0.14	23	100	90,000
N.B.	Werlhof's	0.20		100	44,000
B.V.	Werlhof's	0.14		100	96,000
S.A.R.	Hypersplenism presplenectomy	0.18			54,000
	24 hrs. post-splenectomy	0.16		100	418,000
	7 days post-splenectomy	0.14	16	100	448,000
F.E.O.	Endometriosis Easy bruising	0.14	25	100	108,000
P.O.L.	Easy bruising	0.14		100	
J.P.	Easy bruising	0.14	23		243,000
J.A.N.	Hemophilia	>0.20	128		
S.T.E.	Hemophilia	>0.20	270	100	
Z.U.L.	Hemophilia	>0.20	167	100	
		0.32	260	100	
J.S.	Hemophilia	0.18	58	100	
		>0.20	99	100	
		>0.20	195		204,000
D.O.Y.	Hemophilia	>0.20	180	97	280,000
R.A.	Hemophilia	>0.20	120	86	250,000
G.S.	Hemophilia	>0.20	63	100	
R.O.	Thrombophlebitis dicoumarol Rx.	>0.20	150	10	
B.O.S.	Thrombophlebitis dicoumarol Rx.	0.14	51	86	
H.A.R.	Thrombophlebitis	0.14	18	95	190,000
L.E.N.	Thrombophlebitis	0.14	37	56	
L.W.	Thrombophlebitis	0.14	12	100	
M.I.C.	Chronic nephritis, uremia	0.18	14	95	122,000
M.O.	Chronic nephritis, uremia	0.18	40	87	
B.A.R.	Giant urticaria and edema	0.14	15		
W.S.	Hodgkin's with nitrogen mustard 10 days before	0.14	10	97	58,000
B.U.C.	Postirradiation	0.14	35	96	157,000
P.A.L.	Lupus erythematosis	0.14	30	100	
N.B.	Erythroblastosis 2 hrs. postpartum	0.14	15	(Blood not checked for presence of fibrinogen or prothrombin)	
	30 hrs. postpartum	>0.20	Incoag.		

12) is of interest. They have demonstrated an increased antithrombin titer in 11 of 26 patients with acute leucemia and in certain other diseases. Minot and Denny reported a similar finding in 1 case of splenomyelogenous leucemia. Castex more recently reported on 5 patients with "pseudohemophilia" who had prolonged clotting times, which were shortened but not always returned to normal when protamine sulfate was given.

The bloods of these patients are much more susceptible than normal to the effect of added heparin (2). This decreased tolerance is due primarily to the decreased thromboplastin associated with thrombocytopenia, as indicated by Howell (9) in 1917. However, bloods with reduced prothrombin activity are also more sensitive to the effects of added heparin (1). The protamine titration has been made sufficiently insensitive so that the effects of moderate prothrombin deficiency, heparinization as therapeutically employed, and thrombocytopenia were not in themselves capable of increasing the titration in otherwise normal blood.

The clinical response of these patients to toluidine blue and protamine sulfate does not necessarily imply that these agents are reacting with human heparin. Both of these agents are basic compounds containing amino groups and are capable of reacting with other compounds, many of which are normal body constituents, and some of which are not even heparin-like.

The therapeutic response appeared to be limited to the extent that this clotting defect contributed to the over-all hemorrhagic picture. Good and apparently permanent correction of the hemorrhagic state occurred in the patients listed in Table I. In this group the only detectable abnormalities were the increased protamine titration and the prolonged whole blood clotting time, except for fibrinolysin and moderate prothrombin deficiency as shown in Case 2. Temporary and slower responses occurred in the complicated hemorrhagic states listed in Tables II and III. In these patients, when ulcerations were present, the response was slow and often incomplete; this, presumably, was due to local infection, thrombocytopenia, vascular injury, and continued trauma.

Aminopterin in excessive amounts produces an ulcerative and hemorrhagic enteritis in the normal animal (1). This intestinal bleeding, like that of ulcerative colitis, is primarily local in origin, and neither of these disorders

responds to toluidine blue. Aminopterin therapy also increases the protamine titration and usually prolongs the whole blood clotting time in the normal dog; this process is reversible with toluidine blue.

The prolonged clotting time, increased protamine titration, thrombocytopenia and vascular defect in leucemia, and perhaps in certain other disorders, are probably dependent upon a common defect(s), the nature of which is not known.

The vascular disturbance was probably the most important single defect in the patients listed in Tables II, III, and IV. Petechiae as well as ecchymoses were prominent features in most of these hemorrhagic disorders. While the vascular disorder may be exaggerated by changes in the clotting mechanism, it is probably independent of the prolonged clotting time, because hemophilia and severe prothrombin deficiency with lengthened clotting times do not characteristically produce petechiae.

In a previous report (2) the fact that subcutaneous extravasation of blood was lessened in some cases led us to the erroneous conclusion that toluidine blue improved the vascular defect. Any improvement in spontaneous petechiae formation appears due to changes in the clotting mechanism and not in the vascular wall. Consequently, hemorrhage from vascular defects can be expected to occur and may be disastrous in the case of intracranial hemorrhage, even though toluidine blue has been given and the clotting defects returned to normal.

Toluidine blue and protamine sulfate therapy proved to be of definite value in properly selected cases. In a few instances it may have prolonged the life of the patient. In others it gave palliative relief and lessened the amount of nursing attention required. Its use in improperly studied patients will not only lead to poor clinical results, but may cause withholding from the patient other forms of indicated therapy that might be life-saving. This is especially true in idiopathic thrombocytopenic purpura where splenectomy is the treatment of choice and these agents are only of value in the occasional patient.

SUMMARY

1. A clotting defect is described which is similar but not identical with that produced by the intravenous injection of commercial beef heparin. It is characterized by an increased protamine titration.

2. The clotting defect was found in frequent association with thrombocytopenia and vascular disorders, but these associations apparently were not ones of cause and effect.

3. The defect was found in a variety of diseases, many of which were severe disorders of the hematopoetic system. It also occurred when no hemocytologic or coagulation disorder could be recognized.

4. The defect usually responded to toluidine blue and protamine sulfate administration. Clinical bleeding was influenced only to a degree commensurate with the importance of the plasma defect in the overall picture.

5. The methods of administering toluidine blue and protamine sulfate are presented.

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EXTENSION OF PRIMARY NEOPLASMS OF BONE TO BONE MARROW

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GROSS, in 1879, in his classical paper on bone sarcomas said, "From a practical point of view, it should be remembered that the medulla may be affected not only at the immediate seat of the tumor but at some distance beyond. When it is remembered that not only the soft parts and corresponding portion of the medulla of the bone around which the tumor is seated are liable to be invaded by the morbid product, but that nodules of sarcomatous tissue may exist in the medullary canal at some distance from the original growth, the line of practice to be followed in the periosteal sarcomas is to amputate as far as possible from the seat of the disease as may be consistent with the patient's safety." Since this statement by Gross, many other authors have reported the observance of medullary extension from various types of primary osseous neoplasms and some have taken note of this medullary extension in their discussions of the treatment of bone tumors. However, a search of the literature revealed no evidence of a primary study of the characteristics of extension to bone marrow as displayed by the various individual neoplasms of bone. Accordingly it was decided to study this problem and also the relationship of medullary extension to prognosis, diagnosis, and treatment in various primary tumors of bone.

MATERIALS AND METHODS

The following primary neoplasms of bone were studied: osteogenic sarcomas, Ewing's tumors, and primary chondrosarcomas. The myeloma series of bone neoplasms was not studied because it is well known that a diffuse involvement of the bone marrow is usually present and also because of the lack of proper material for study since amputation is rarely performed in these cases. Study of the vascular neoplasms of bones was confined to Ewing's tumor or malignant hemangioendothelioma of bone (Broders' classification). Although periosteal fibrosarcomas are known to invade the medullary cavity secondarily they are not a primary neoplasm of bone and were not included in this study. The so-called endosteal fibrosarcomas have been classified as fibroblastic types of osteogenic sarcoma and will be discussed under this heading. The controversial malignant giant-cell sarcoma was not studied. No case of liposarcoma, reticulum-cell sarcoma, lymphosarcoma, erythroblastoma, chloroma, or adamantinoma was included either because of its rarity or obvious behavior as regards bone marrow extension. Metastatic lesions of bone were not considered.

The tumors selected for study were located in the long bones of the extremity. Material was obtained from extremities amputated prior to death in all cases. The basis for selection was that the tumor be located in a long bone and that the entire extent of the amputated specimen had been suitably preserved. Unfortunately many specimens had been ruined for purposes of this study by the discarding of bone and soft tissue proximal and distal to the lesion in order to conserve storage space, or by the longitudinal sectioning of the bone which had allowed disintegration of the bone marrow. The actual location of the tumor in the long bone, site of amputation, period of survival, grade of malignancy, or in the cases of osteogenic sarcoma, the predominant cell type, were not factors considered in the selection of specimens but were considered as the study progressed. Our study consisted of

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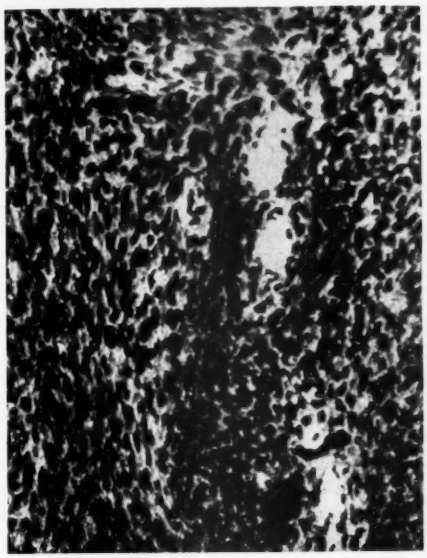

Fig. 1. Appearance of osteogenic sarcoma, fibroblastic type. New bone formation is not seen in this section but was present in other areas of the tumor (hematoxylin and eosin, ×160).

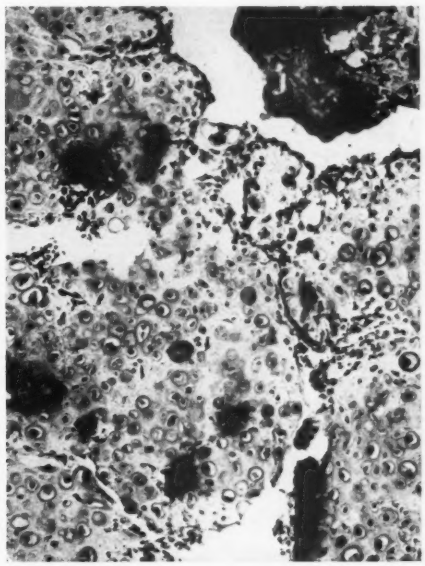

Fig. 2. Osteogenic sarcoma, chondroblastic type. The predominance of cartilage cells and hyaline matrix with new bone formation is characteristic of the chondroblastic type of osteogenic sarcoma (hematoxylin and eosin, ×80).

gross and microscopic examinations of the bone marrow in specimens available in 50 cases of osteogenic sarcoma, 20 of Ewing's tumor, and 5 of primary chondrosarcoma. In each, the soft tissue was dissected from the bone containing the lesion and the limits of cortical involvement as seen grossly were measured carefully and recorded. The remainder of the bone was then examined for evidence of medullary extension past the confines of the cortical involvement. The gross features indicating involvement of the bone marrow were noted and the amount of medullary extension as seen grossly past the confines of cortical involvement were measured carefully and recorded.

Specimens were taken from the bone marrow for microscopic study at regular short intervals throughout the length of the bone containing the lesion, and the location of each specimen with regard to the bone and to the gross confines of the cortical and medullary lesion was noted. Slides were made from these specimens and these were examined. The limits of medullary involvement were determined by microscopic study. Slides of the main lesion also were examined and the type of neoplasm and grade of malignancy were established carefully. Only Ewing's tumors were not graded.

Osteogenic sarcomas were divided into the subtypes of fibroblastic, chondroblastic, or osteoblastic on the basis of the predominant cell appearing in the lesion. In most cases all three types of cells could be demonstrated, but in every instance, one of the three types of cells was predominant and determined the type of osteogenic sarcoma. While the basis for classification of the fibroblastic (Fig. 1) and chondroblastic (Fig. 2) groups is evident, some explanation may be due in regard to the cases placed in the osteoblastic (Fig. 3) group. The osteoblastic group was characterized by a histologic picture showing myriads of osteoblasts, new bone spicules, an osteomucoid or osteoid matrix, and anastomosing trabeculae of well formed bone; the picture predominantly was that of osteoblastic or bone-forming

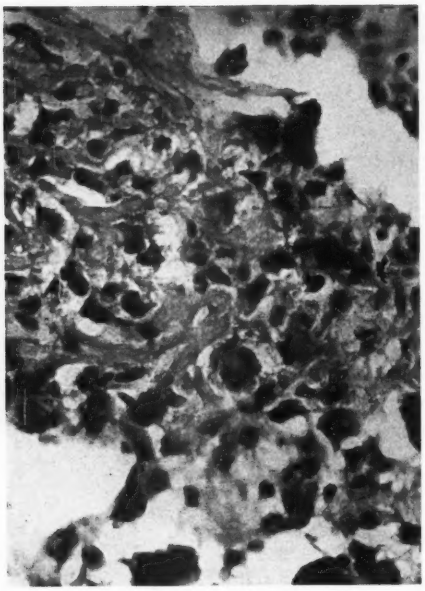

Fig. 3. Osteoblastic type of osteogenic sarcoma (hematoxylin and eosin, ×310).

activity. This classification is not original with us, having first been described in 1943 by MacDonald and Budd, and prior to these authors' paper, Simmons made a similar classification of the osteogenic sarcomas, in which he divided them into fibroblastic, chondroblastic, and anaplastic varieties. The reasons for the division of the osteogenic sarcomas into these three predominant cell types was to see whether the characteristics of medullary extension differed in the three types. That there is a definite difference in the prognosis in the osteosarcomas of various cell types and that osteoblastic or "osteosarcoma" described by MacDonald and Budd has the worst prognosis, had been well established by these authors before our study was begun.

In an attempt to determine whether or not there was any correlation between the location of the primary lesion and its tendency toward medullary extension, the amounts of medullary extension exhibited by tumors located in the lower part of the tibia or fibula, upper part of the tibia or fibula, lower part of the femur, upper part of the femur, lower part of the radius or ulna, upper part of the radius or ulna, lower part of the humerus, and upper part of the humerus were compared for each of these bones.

The grade of malignancy was compared with the amount or extent of medullary extension in each of the cases of osteogenic sarcoma and chondrosarcoma in order to determine whether there was any relation between the grade of malignancy and the tendency toward bone marrow invasion. Ewing's tumors as said previously were not graded.

The limits of medullary involvement as seen on the preoperative roentgenograms were measured as accurately as possible and compared to the amount of extension found by gross and microscopic study of the medullary cavity of the specimen. The roentgenograms had been discarded in some of the earlier cases so that this comparison was not entirely complete but fortunately could be made in the majority of the cases.

Follow-up data were obtained in most of the cases. The following facts were ascertained as completely as possible for each patient: period of survival after amputation; if the patient was deceased, the date and cause of death were obtained; if he was living, evidence indicative of metastasis was sought. After these facts were obtained, an attempt was made to correlate neoplastic medullary extension with survival rate in each of the types and subtypes of neoplasm studied. The end results obtained in cases in which amputation had been performed across the bone containing the lesion were compared to the end results in cases in which the extremity had been removed by disarticulation of the joint or amputation across the bone proximal to the bone containing the lesion; this comparison was made in the cases of osteogenic sarcoma, Ewing's tumor, and chondrosarcoma, respectively.

The final portion of this work consisted of a statistical study of a separate group of cases of osteogenic sarcoma in an attempt to determine whether some of the observations made in the 50 cases of osteogenic sarcoma selected for the primary study were statistically significant. In the original cases of osteogenic sarcoma studied, it was found that when am-

putation had been carried out through the next higher bone or joint above the bone containing the lesion a higher percentage of patients survived for 5 years than did the group in which amputation was across the bone containing the lesion. Accordingly, it was decided to determine whether or not a larger series of cases would give similar results. The records in all cases of osteogenic sarcoma encountered at the Mayo Clinic between the years 1910 and 1935 were examined and all cases satisfying the following criteria were chosen for study. The lesion had been located in the humerus, radius, ulna, femur, tibia, or fibula; treatment had been amputation of the extremity; and finally complete follow-up history was available. Cases in which metastatic lesions were known to be present before operation were excluded. Ninety-five cases were found to satisfy these conditions, 7 of which had been included in the primary study. The remaining 88 cases were divided according to whether amputation had been by transection through the bone containing the lesion or by disarticulation of the proximal joint or amputation through the bone proximal to the bone containing the lesion. The survival rates in these two groups of cases were then compared.

FINDINGS

The gross appearance of the neoplastic involvement of the medullary cavity was similar to that of the principal lesions in almost all cases. For example, in the chondroblastic types of osteogenic sarcoma, the medullary lesion was of an osteocartilaginous nature. The variations in gross appearance of these tumors has been described at length in several textbooks and our observations corresponded with these previous descriptions. In the osteogenic sarcoma the entire circumference of the bone marrow was usually grossly involved at the point of the principal or cortical lesion, while as one progressed away from this point, medullary extension, if it occurred, tended to be along one wall or segment of the circumference of the medullary canal. The medullary extension occurring in the fibroblastic type of osteogenic sarcoma was particularly likely to spread in this manner, a small tongue-like projection being seen along one wall for several inches in some cases. In the osteogenic sarcomas gross medullary extension was usually easy to see if it occurred, the neoplastic tissue being sharply delineated from the normal bone marrow. Medullary extension seen in Ewing's tumors was diffuse, involving the entire diameter of the medullary canal as it progressed away from the main lesion. The extension of Ewing's tumor was always of a soft, vascular nature without definite borders, and the extent of medullary involvement was difficult to determine grossly as tumor tissue faded indefinitely into normal bone marrow. The primary chondrosarcomas observed failed to exhibit any medullary extension that could be discerned by gross or microscopic examination. In all the cases studied regardless of type, the cartilaginous epiphyseal plate was noted to present an effective barrier to neoplastic extension, erosion and extension through this structure being seen only infrequently.

The microscopic appearance of neoplastic extension was the same as that of the main lesion; even the smallest microscopic projections usually exhibited the morphologic and cellular characteristics of the principal lesion. A tendency for the neoplastic cells to extend along one segment of the endosteal surface of the cortex was noted in the osteogenic sarcoma on microscopic, just as in gross, examination. In these cases, a search for malignant cells made about the periphery or circumference of the bone marrow yielded much better results than a search of the central portion, as extension was rarely seen in the central area without finding it at the periphery of the bone marrow next to the cortex for an even greater distance away from the principal lesion. In Ewing's tumor, medullary extension, being of a diffuse character, was likely to be seen all through or in any part of a cross section of the bone marrow. Invasion of, and extension along, the haversian canals in the cortex was noted in many instances, particularly in Ewing's tumors, but in no case was extension in a haversian canal found to exceed medullary extension in distance from the principal lesion. Some tendency for the lesion to extend along the outside of blood vessels was noted, particularly in the fibroblastic type of osteogenic sarcoma. In some instances plugs of tumor

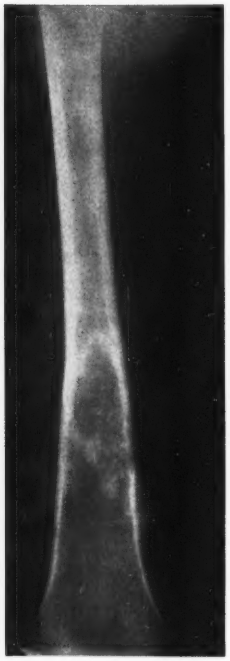

Fig. 4. Osteoblastic type of osteogenic sarcoma of the lower part of the femur with roentgenologic evidence of medullary involvement extending only to the midshaft.

tissue were seen inside blood vessels in the bone marrow and accounted for one of the sources of distant metastasis found in primary sarcoma of bone. No barrier inhibiting medullary extension, such as a fibrous wall or capsule, was found in any specimen studied.

In all cases studied regardless of type or subtype, direct extension was responsible for medullary involvement. In no cases could a defect in the continuity of the medullary neoplastic progression away from the principal

TABLE I.—AMOUNT OF MEDULLARY EXTENSION FOUND IN CASES OF OSTEOGENIC SARCOMA

Medullary extension	Cases	Per cent
Beyond cortical lesion		
1 to 3 inches (gross + microscopic evidence)	10	20
3 inches or more (gross + microscopic evidence)	10	20
None found	30	60
Total	50	100

TABLE II.—AMOUNT OF MEDULLARY EXTENSION FOUND IN THE PREDOMINANT CELL TYPES OF OSTEOGENIC SARCOMA

Medullary extension	Predominant cell type					
	Fibroblastic		Chondroblastic		Osteoblastic	
	Cases	Per cent	Cases	Per cent	Cases	Per cent
Gross + microscopic evidence 1 to 3 inches	13	39	3	43	4	40
3 inches or more	6	18	0		4	40
No medullary extension	14	43	4	57	2	20
Total	33	100	7	100	10	100

lesion be definitely established either by gross or microscopic examination of the bone marrow.

In regard to the actual amount of extension (Table I) one-fifth of the osteogenic sarcomas studied revealed pronounced extension in the bone marrow varying from 3 inches (7.6 cm.) past the limits of the cortical lesion to an involvement of the entire shaft. In another fifth of the cases extension of 1 to 3 inches (2.5 to 7.6 cm.) was present and in the remaining three-fifths no medullary extension could be demonstrated. On microscopic examination medullary extension of 3 inches or more past any evidence of the lesion as seen grossly was found in 18 per cent of cases. Of the osteogenic sarcomas (Table II) the osteoblastic type showed the greatest tendency, the fibroblastic type the next to greatest, and the chondroblastic type the least tendency to medullary extension. Ewing's tumors displayed a greater tendency to extension to the bone marrow than either the osteogenic sarcomas or chondrosarcomas. Forty-five per cent of Ewing's tumors extended 3 inches or more past the cortical lesion; in 6 cases (two-thirds of this group or 30 per cent of the total group) the entire medullary cavity was involved. In 30 per cent of the cases of Ewing's tumor extension for 1 to 3 inches had occurred, and in the remaining 25 per cent, no extension was found. No extension was found past the limits of gross cortical involvement in any of the cases of primary chondrosarcoma studied.

The actual position of the main lesion in the bone was found to be of no particular value in

TABLE III.—ROENTGENOLOGIC EVIDENCE OF MEDULLARY EXTENSION COMPARED WITH MICROSCOPIC EVIDENCE OF MEDULLARY SPREAD

Evidence of medullary extension	Osteogenic sarcoma		Ewing's tumor		Chondrosarcoma	
	Cases	Per cent	Cases	Per cent	Cases	Per cent
Roentgenologic and microscopic same	29	69	4	44	4	100
Microscopic exceeded roentgenologic	13	31	5	56	0	
Total (with suitable roentgenograms)	42	100	9	100	4	100

predicting whether or not medullary extension would occur. However, in the osteogenic sarcomas, the incidence of extension up the medullary cavity from lesions of the lower part of the femur was greater than the incidence of spread down the medullary canal from lesions located in the upper part of the tibia. The reason for this cannot be explained.

In the osteogenic sarcoma group the greatest amount of medullary extension was found in the higher grades of malignancy. Medullary extension of 3 inches or more was found in 25 per cent of lesions of grade 3 malignancy and in 29.3 per cent of the lesions of grade 4, but extension was less than 3 inches in all cases in which lesions of grade 1 and grade 2 were present. This was an expected finding in view of the greater invasive tendency and rate of mitosis exhibited by higher grades of malignancy. However, the grade of malignancy made no difference in the amount of extension in the chondrosarcoma group, none being found regardless of grade. Ewing's tumors were not graded.

The results obtained in the comparisons made between the amount of medullary extension evident on the preoperative roentgenograms as against the amount of medullary extension actually found by gross and microscopic study of the amputated extremities are given in Table III. The distance by which microscopic extension exceeded roentgenologic evidence of medullary involvement was recorded in each of the cases showing this difference and varied from 1 inch (2.5 cm.) to an involvement of the entire shaft above the lesion as seen roentgenologically (Figs. 4 and 5).

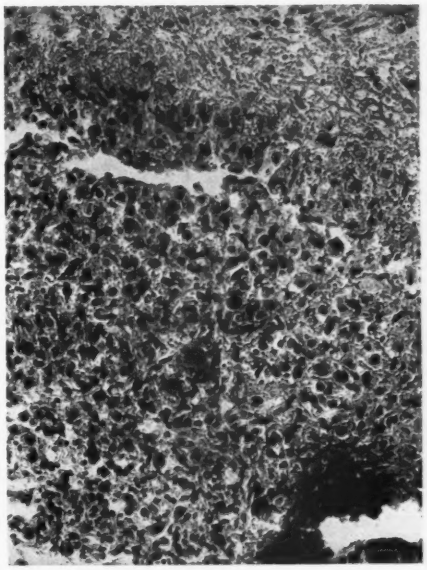

Fig. 5. Medullary material removed from the femur shown in Figure 4. This section was from the intertrochanteric region and shows that the sarcoma has extended throughout the medullary cavity of the involved femur (hematoxylin and eosin, ×120).

Survival periods following the date of amputation have been compared with the amount of medullary extension found on gross and microscopic examination. These results are given in Table IV. Those cases in which adequate follow-up data could not be obtained or in which the postoperative period was less than 3 years at the time of this study were excluded. The patient who was free from clinical or roentgenologic evidence of metastasis or recurrence of the lesion in the stump was classed as well. Data on the primary chondrosarcomas are not included in Table IV. Of the 5 patients studied, none had any medullary extension, 1 patient was considered cured, 1 died 1 year after operation, 2 were living and well but the postoperative period was less than 3 years, and 1 patient could not be traced.

The survival rates in cases in which amputation was carried out through the bone containing the lesion were compared with those in cases in which disarticulation or amputation through the bone proximal to the bone con-

TABLE IV.—COMPARISON OF SURVIVAL RATE WITH AMOUNT OF MEDULLARY EXTENSION

Lesion and medullary extension	Results after operation								
	Dead or with known metastasis				Living and well 3 to 5 years		Living and well 5 years or more		Total (with adequate follow-up)
	Less than 3 years		3 to 5 years						
	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	
Osteogenic sarcoma									
No extension	14	61	3	13	3	13	3	13	23
Extension 1 to 3 in.	7	88	1	12	0		0		8
Extension 3 in. or more	5	71	0		1	14	1	14	7
Ewing's tumor									
No extension	1	17	1	17	1	17	3	50	6
Extension 1 to 3 in.	4	80	0		1	20	0		5
Extension 3 in. or more	7	78	1	11	0		1	11	9

taining the lesion was performed. The results are shown in Table V for the entire series of cases and in Table VI for the cases in which the various predominant cell types of osteogenic sarcoma were present. Patients were listed as cured who were living and well 5 years from the date of amputation and who had no clinical or roentgenologic evidence of metastasis. Not evident in the tables is the fact that of 6 patients who underwent disarticulation or hemipelvectomy for osteogenic sarcoma of the femur 1 died 6 months after operation, 2 patients were considered cured, 1 being alive and well 16 years after operation and the other 7 years after operation, and the 3 remaining patients were living and well, but less than 3 years had elapsed since the date of amputation.

The results obtained from the statistical study on the 88 additional cases of osteogenic sarcoma, which were selected as described previously in this paper, are contained in Table VII.

COMMENT

The lack of evidence suggesting that multiple foci of medullary involvement might evolve by the process of embolism from a primary sarcoma located in the same bone, and the demonstration of direct extension as the means by which a primary bone sarcoma spreads in the bone marrow, was interesting. It has been established that the capillaries and blood vessels conducting blood in the bone marrow are closed structures and not in communication with the parenchyma of the bone marrow (1, 2). Therefore, malignant cells making their way through the walls of blood vessels in the medullary cavity evidently are conducted out of the medullary cavity to some distant point of the body rather than setting up a new focus of medullary involvement in the same bone. There was no evidence to suggest that spread had occurred through the lymphatics of bone marrow in any of the cases studied. Direct extension being the method of medullary spread from a primary bone sarcoma, the actual position of the neoplasm should have little influence on the incidence or amount of medullary extension that occurs. Accordingly lesions located in either the proximal or distal end of the bone were found to spread comparable distances down or up the medullary cavity as the case might be and lesions of the shaft extended in either direction.

An interesting fact was that in 10 of the 50 cases of osteogenic sarcoma studied (an incidence of 20 per cent) medullary extension was found for 3 inches or more past any cortical evidence of the lesion. In 3 of the 10 cases medullary extension was found to the point of amputation. In these 3 cases there was no record that microscopic examination of the bone marrow had been made at the time of amputation. Medullary extension was found by microscopic means 3 inches or more past any gross evidence of medullary involvement in 18 per cent of the cases of osteogenic sarcoma. This fact indicates that gross inspection of the bone marrow for evidence of medullary extension at the point of amputa-

TABLE V.—RESULTS AFTER AMPUTATION THROUGH BONE CONTAINING LESION AND PROXIMAL TO BONE CONTAINING LESION

Site of amputation and result	Osteogenic sarcoma		Ewing's tumor		Chondrosarcoma	
	Cases	Per cent	Cases	Per cent	Cases	Per cent
Through bone with lesion Follow-up adequate	19		6		2	
Postoperative survival: 3 yr. or more*	5	26	4	67	1	50
5 yr. or more*	2	11	2	33	1	50
Cures	1	5	2	33	1	50
Proximal to bone with lesion Follow-up adequate	19		13		0	
Postoperative survival: 3 yr. or more*	7	37	4	31	0	
5 yr. or more*	4	21	2	15	0	
Cures	3	16	2	15	0	

*Patients considered cured included.

TABLE VI.—PREDOMINANT CELL TYPES OF OSTEOGENIC SARCOMA: RESULTS AFTER AMPUTATION THROUGH BONE CONTAINING LESION AND PROXIMAL TO BONE CONTAINING LESION

Site of amputation and result	Predominant cell type of osteogenic sarcoma					
	Fibroblastic		Chondroblastic		Osteoblastic	
	Cases	Per cent	Cases	Per cent	Cases	Per cent
Through bone with lesion Follow-up adequate	13		3		3	
Postoperative survival: 3 yr. or more*	4	31	1	33	0	0
5 yr. or more*	1	8	1	33	0	0
Cures	0	0	1	33	0	0
Proximal to bone with lesion Follow-up adequate	11		4		4	
Postoperative survival: 3 yr. or more*	4	36	3	75	0	0
5 yr. or more*	3	27	1	25	0	0
Cures	2	18	1	25	0	0

*Patients considered cured included.

tion is not sufficient, and that in those cases in which amputation has been performed through the bone containing the lesion, the surgeon should insist on microscopic examination of the bone marrow before deciding that the point of amputation is high enough. As was expected, the greatest incidence of medullary spread was found in cases of Ewing's tumor; the entire medullary canal was involved in 30 per cent of the cases. Too few cases of primary chondrosarcoma in the long bones were studied to permit positive statements, but the finding of no medullary extension, either by gross or microscopic means, in the 5 cases studied, suggests that the tendency toward medullary extension is much less in this form of primary bone neoplasm than in other types. The fact that in none of the cases of osteogenic sarcoma of chondroblastic type studied was medullary extension of 3 inches or more evident, also would seem to support the contention that cartilaginous neoplasms of bone show the least tendency toward medullary extension.

In the cases of osteogenic sarcoma comparison of survival rates with the amount of medullary extension failed to reveal any significant differences in the survival periods in cases in which no medullary extension was found and in cases in which marked medullary extension was present. This finding is of significance in that it tends to show that the incidence of distant metastasis is not increased regardless of the amount of medullary extension. Invasion of blood vessels and distant metastasis occur with about the same frequency in cases in which medullary involvement is confined to the region of the cortical lesion as in cases in which lesions have spread along the bone marrow. It was thought that the incidence of distant metastasis might be increased in cases in which medullary extension was present and be reflected in a lower survival rate in these cases. The reason for this opinion was that the lesion which extends in the medulla surrounds a larger amount of the blood vessels in the bone marrow and a larger surface area is presented for invasion of the vessels. In this study, however, the results obtained seem to indicate that if amputation is carried out proximal to the lesion, the effect of medullary extension, regardless of amount, on the survival rate is nullified.

Our study of Ewing's tumor on the contrary, revealed a significant difference in the survival rates in cases in which no medullary

TABLE VII.—RESULTS AFTER AMPUTATION THROUGH BONE CONTAINING LESION AND PROXIMAL TO BONE CONTAINING LESION IN 88 CASES OF OSTEOGENIC SARCOMA*

Result	Amputation through bone containing lesion		Amputation proximal to bone containing lesion	
	No.	Per cent	No.	Per cent
Died less than 3 yr. postoperative	36	78	21	50
Postoperative survival of: 3 to 5 yr.†	3	7	3	7
5 yr. or more†	7	15	18	43
Cures	6	13	13	31
Total cases	46	100	42	100

*Cases selected as described in text.
†Patients considered cured included.

extension was present from those in which medullary extension had occurred. Sixty-six per cent of the patients who did not have any medullary extension were living and well 3 years after operation and 50 per cent were considered cured by the amputation. Of the patients who had medullary extension of 3 inches or more, only 11 per cent were living and well 3 years after operation, and 11 per cent were considered cured. These results tend to show that in cases of Ewing's tumor the greater the invasive tendency, as shown by the amount of medullary spread, the poorer the prognosis. Presumably this is because of a higher incidence of blood vessel invasion with distant metastasis in the cases in which medullary extension is increased.

If the surgeon could be sure that the point of amputation was above the most proximal point of a primary bone sarcoma, then the dictum of never amputating through the bone containing the lesion unless absolutely necessary would be invalid, and the end results of transection through the bone containing the lesion and disarticulation at the joint or amputation through the bone proximal to the bone containing the lesion should not differ. The surgeon, however, is confronted by many obstacles in determining whether or not the site of amputation is proximal to the lesion, if he chooses to amputate through the bone containing the lesion rather than above it. Roentgenograms may not portray the medullary extension that is present. Gross examination of the bone marrow at the point of amputation may give an erroneous impression as microscopic medullary extension often exceeds any medullary extension that can be seen grossly. The number of errors that are made in this determination is well demonstrated by the poorer results (Tables V and VII) found in the cases of osteogenic sarcoma in which transection was done through the bone containing the lesion than in those in which disarticulation or amputation through the bone proximal to the bone containing the lesion was done. The better results obtained by the radical amputation above the bone containing the lesion take on added significance when it is remembered that the most advanced lesions showing the most involvement of cortical and soft tissues were almost always in the group treated by amputation or disarticulation proximal to the bone containing the lesion. The better prognosis offered by amputation proximal to the bone containing the lesion, is no doubt due in part to the fact that the higher amputation increases the incidence in which amputation is above the most proximal neoplastic infiltration of soft or subperiosteal tissue. An even more important factor in the better prognosis offered by the more radical surgical procedure is believed to be the fact that amputation is certain to be above the highest medullary extension of the neoplasm. Of the 14 patients who had osteogenic sarcoma treated by transection through the bone containing the lesion and who survived less than 3 years, 3 (21 per cent) displayed microscopic evidence of medullary neoplasm at the point of amputation. The failure to find more cases of extension to the site of amputation in this group is believed due to the difficulty in demonstrating malignant changes in individual cells, or in small clusters of cells which lack the morphologic arrangement of the main lesion, in the bone marrow of specimens preserved in formalin for several years. Exact information regarding the incidence of local recurrence in the amputation stump could not be obtained, but the fact that local recurrence is known to have occurred in at least 1 of the cases in which malignant change could not be found at the proximal end of the amputated specimen tends to support the view that

malignant cells were present at the site of amputation in a higher percentage of cases than could be demonstrated in the specimens available for this study.

Comparison of the end results obtained by transection through the bones containing the lesion with those obtained by higher amputation was interesting in cases of the various cell types of osteogenic sarcoma. The fibroblastic and chondroblastic types gave findings in keeping with the results discussed for the osteogenic sarcoma group as a whole. When amputation had been performed through the proximal bone or through the joint proximal to the lesion results were much better than when transection had been done through the bone containing the lesion. In the osteoblastic type of osteogenic sarcomas these findings did not apply. No patient survived for 3 years after operation regardless of the site of amputation. This finding is in keeping with the observations of MacDonald and Budd. These authors in 1943 published the results of a study of the 118 five year cures in cases of osteogenic sarcoma listed in the bone sarcoma registry of the American College of Surgeons. They divided these cases into fibroblastic, chondroblastic, and osteosarcoma subtypes and stated, "A comparative analysis of the cases of cured and uncured osteogenic sarcoma indicates that true osteosarcoma is an almost uniformly fatal form of neoplasm, accounting for but a fraction of the cures." Their description of the histologic features of osteosarcoma corresponds to those of the lesion called "osteoblastic type of osteogenic sarcoma" in our study. Apparently the osteoblastic type of osteogenic sarcoma invades blood vessels much sooner than the fibroblastic or chondroblastic types and metastasis has occurred before the patient comes to surgery in the majority of cases.

The percentage of 5 year survivals and patients cured was twice as great in the cases of Ewing's tumor in which transection was performed through the bone containing the lesion as in the group in which amputation was carried out proximal to the bone containing the lesion. In view of the exactly opposite results in cases of the osteogenic sarcoma, this seemed unusual. Inspection of the 6 cases in which transection through the bone containing the lesion was performed revealed that in 4 there was medullary extension of less than 1 inch, and in 2 of more than 3 inches; in 1 of these last 2 cases medullary extension was demonstrated at the site of amputation. In 7 of the 13 cases in which the limb was amputated proximal to the bone containing the lesion, medullary extension was marked; in 6 the entire shaft was involved. In 3 cases there was medullary extension of 1 to 3 inches, and in 3 no medullary extension. The 3 patients who had no medullary extension were living and well, 10, 7, and 3 years after operation, respectively. It was observed in a previous paragraph that the prognosis was poorer in cases of Ewing's tumors with marked medullary extension than in cases with little such extension, presumably because the lesions showing the greater invasive tendency, as reflected by medullary extension, also invade the blood vessels and metastasize earlier and more often than do less invasive lesions. Probably this factor is the one responsible for the failure to obtain better results in the group of Ewing's tumors treated by removal of the extremity proximal to the bone containing the lesion than were obtained in the group treated by transection of the bone containing the lesion.

CONCLUSIONS

From this study the following conclusions were drawn:

1. Direct extension is the usual method by which a primary bone sarcoma spreads in the bone marrow from its initial location in a long bone.

2. Medullary extension from a primary bone sarcoma may occur without roentgenologic evidence of its presence.

3. Neoplastic medullary involvement may be found on microscopic examination for a considerable distance past any gross evidence of medullary extension in many cases of primary bone sarcoma.

4. Of the primary bone neoplasms studied, Ewing's tumor exhibited the greatest tendency, osteogenic sarcomas the next greatest, and primary chondrosarcomas the least, to spread in the bone marrow. In this series, 45 per cent of Ewing's tumors, 20 per cent of

osteogenic sarcomas, and none of the primary chondrosarcomas showed medullary extension for 3 inches or more past the limits of cortical involvement by the lesion.

5. Of the predominant cell types of osteogenic sarcoma, the osteoblastic type exhibits the greatest tendency, the fibroblastic type the next greatest, and the chondroblastic type the least, to extend in the bone marrow.

6. In osteogenic sarcoma, the higher the grade of malignancy, the greater the amount of medullary involvement that is likely to be found. In this study no medullary extension was found in cases of primary chondrosarcoma regardless of grade of malignancy and no attempt was made to grade malignancy in Ewing's tumors.

7. The amount of medullary extension per se cannot be used as a basis for prognosis in osteogenic sarcoma; while in Ewing's tumors, cases with marked medullary involvement have a distinctly worse prognosis. Apparently invasion of blood vessels and metastasis is as likely to occur in cases in which osteogenic sarcomas show no spread in bone marrow as in those in which marked medullary extension occurs past the confines of the cortical lesion. In Ewing's tumors, however, those which have a greater invasive tendency as reflected by increased medullary extension, are more likely to invade blood vessels early and have caused undetected metastatic lesions at the time of surgery.

8. In the treatment of primary bone sarcoma by amputation, microscopic examination of the bone marrow at the point of amputation should be mandatory in every case in which amputation is performed through the bone containing the lesion before the surgeon concludes that the amputation is proximal to the lesion. The recognition of malignant cells individually or in small clusters may be very difficult, and when any doubt exists, amputation should be performed at a higher level. In this study the inadequacy of roentgenologic and gross methods of examination used alone for the detection of extension in the bone marrow was illustrated in the study of the survival rates in cases of the osteogenic sarcomas. Microscopic examination of the bone marrow at the site of amputation was not routine in these cases. It was found that in the cases of osteogenic sarcoma in which amputation was proximal to the bone containing the lesion results were superior to those in cases in which transection was carried out through the bone containing the lesion. One important cause of the poor results of amputation through the bone containing the lesion, as compared to the results of amputation above the affected bone, was failure to amputate proximal to the lesion, since the amputation occasionally was through an area of medullary extension which was undetected at the time of surgery.

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CEREBRAL BLOOD FLOW AND METABOLISM IN TOXEMIAS OF PREGNANCY

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IN 1945 Kety and Schmidt (12) reported the determination of cerebral blood flow in man with a technique which permitted the quantitative clinical measurement of this important physiologic function. The safety and significance of this method (9) have since been established by studies on normal young men (14) as well as on groups of individuals with varied pathologic states (10, 11, 13, 15, 16). The development of this procedure makes it possible for the first time for the clinician to study certain phases of the dynamics of disease entities which may in some degree affect intracranial physiology.

Toxemia of pregnancy is typically manifest by symptoms referable to the brain. While much has been postulated concerning the cause and mechanism of this effect, actually very little indeed is known concerning the pathologic physiology of this organ which hitherto had been inaccessible to significant study. It was therefore thought worth while to use the new method in the study of toxemia of pregnancy as well as of normal pregnant women (18).

METHOD

The method is based upon the fact that if the nitrous oxide concentration be determined in arterial and cerebral venous blood for a 10 minute period from the beginning of inhalation of a low concentration of this gas, curves will be obtained as exemplified by the typical one in Figure 1. The venous concentration curve is a fairly complex function of the arterial curve and the cerebral blood flow. From these curves the cerebral blood flow can be calculated by the application of the Fick principle. This postulates, in its simplest form, that the quantity of any substance taken up in a given time by an organ from the blood which perfuses it is equal to the total amount of substance carried to the organ by the arterial inflow less the amount removed by the venous drainage during the same period of time. It has been shown that the cerebral blood flow (CBF) can be calculated from the following formula:

$$CBF = \frac{100\ V_{10} S}{10 \int_0 (A - V)\, dt}$$

Where V = Venous N_2O concentration
V_{10} = Venous N_2O concentration at 10 minutes
A = Arterial N_2O
S = Partition coefficient of N_2O between the brain and blood

$\int_0^{10} (A - V)dt$ = The area between the arterial and the venous curves, over the ten minute period.

This expresses CBF as cubic centimeters of blood flow per 100 grams of brain per minute.

A gaseous mixture, consisting of 15 per cent nitrous oxide, 21 per cent oxygen, and 64 per cent nitrogen, is administered through a tightly fitting mask equipped with inspiratory and expiratory valves. For taking accurately timed arterial blood samples from artery and internal jugular vein, manifolds of 3 way stopcocks have been found to be very convenient (Fig. 2). Transparent plastic tubing connects the manifold to the needle and heparin is used in the system to prevent clotting. The first needle is placed into the superior bulb of the internal jugular vein after infiltration with procaine. The second needle is placed into the femoral artery. No untoward reaction or complication has accompanied this procedure.

Five samples of blood are taken simultaneously from the arterial and venous systems at regular intervals over a period of 10 minutes during which time the nitrous oxide mixture is administered. The heparin tipped syringes are sealed and placed in cracked ice immediately. The mean arterial blood pressure is

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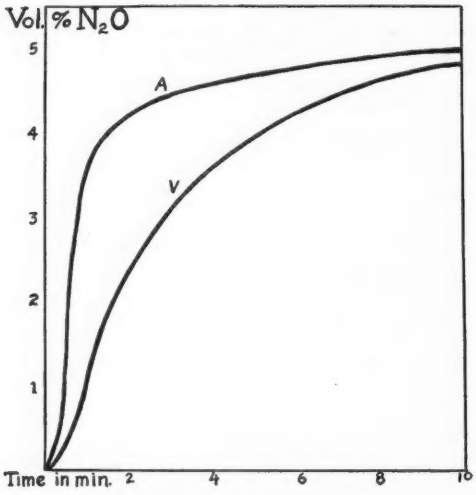

Fig. 1. Typical arterial, *A*, and internal jugular, *V*, curves of nitrous oxide concentration during a 10 minute period of inhalation of 15 per cent nitrous oxide.

taken directly from the femoral artery. The specimens are analyzed for nitrous oxide, oxygen, and carbon dioxide in the manometric Van Slyke apparatus (9).

From these analyses several studies of cerebral metabolism and circulation are made possible. First, as pointed out, the actual cerebral blood flow may be determined. Second, the rate and amount of oxygen utilized by the brain may also be ascertained. This is called the cerebral metabolic rate in terms of oxygen and is determined by the formula:

$$\text{CMR } O_2 \text{ in c.c. of } O_2/100 \text{ gm. brain/min.} = \text{CBF} \times \frac{(A-V)O_2}{100}$$

A third very important function which is made possible of evaluation is the cerebral vascular resistance. A satisfactory approximation is made by the formula:

$$\text{C V R in mm. Hg/c.c./100 gm. brain/min.} = \frac{\text{Mean arterial blood pressure}}{\text{CBF}}$$

This convenient unit represents the pressure necessary to force 1 cubic centimeter of blood per minute through 100 grams of brain.

Fourth, the respiratory quotient of the brain may be measured. It will be recalled that the RQ represents the ratio of the volume of carbon dioxide produced by a tissue to the volume of oxygen absorbed. This is ascertained by the formula:

$$\frac{(V-A)Co_2}{(A-V)o_2}$$

Finally, it is possible to calculate the so-called nutritive index of the brain which is determined by the formula:

$\frac{Ao_2}{(A-V)o_2}$ This represents the ratio between the amount of oxygen offered to the brain and how much it actually uses.

NORMALS

The first problem was to establish the normal values for pregnant women in each of these measurable functions of cerebral circulation and metabolism. Kety and Schmidt (14) had studied 14 normal young men. The mean values obtained in these cases were compared[1] with mean values which were determined from the study of 9 normal young women who were between 34 and 40 weeks' gestation.

TABLE I

	Normal young men	Normal pregnant women
Mean arterial blood pressure	86	90.5
Arterial oxygen in vol. per cent	18	13.4
Arterial carbon dioxide in vol. per cent	49	40.0
Venous oxygen in vol. per cent	11.7	6.9
Venous carbon dioxide in vol. per cent	55	46.2
Arteriovenous oxygen difference in vol. per cent	6.3	6.5
Respiratory quotient of the brain	0.99	0.98
Cerebral blood flow	54	56
Cerebral metabolic rate in terms of oxygen	3.3	3.5
Cerebral vascular resistance	1.6	1.6
Nutritive index of the brain	2.8	2.1

It is at once obvious in Table I that the arterial and venous concentrations of oxygen as well as carbon dioxide are much lower in normal pregnant women than in normal males. The arterial oxygen content in these pregnant women close to term is 26 per cent

[1]Fisher's table of t was used throughout this study to test the significance of difference between normal pregnant women and normal young males as well as between normal pregnant women and patients with the various types of toxemia of pregnancy. The formulae followed were:

$$\text{Standard deviation } (\sigma) \text{ of difference} = \sqrt{\frac{\Sigma_1(d^2)+\Sigma_2(d^2)}{(N_1-1)+(N_2-1)}}$$

$$\text{Significance of difference (t)} = \frac{\text{Difference between means}}{\sigma \text{ of Difference}} \times \sqrt{\frac{N_1 N_2}{N_1+N_2}}$$

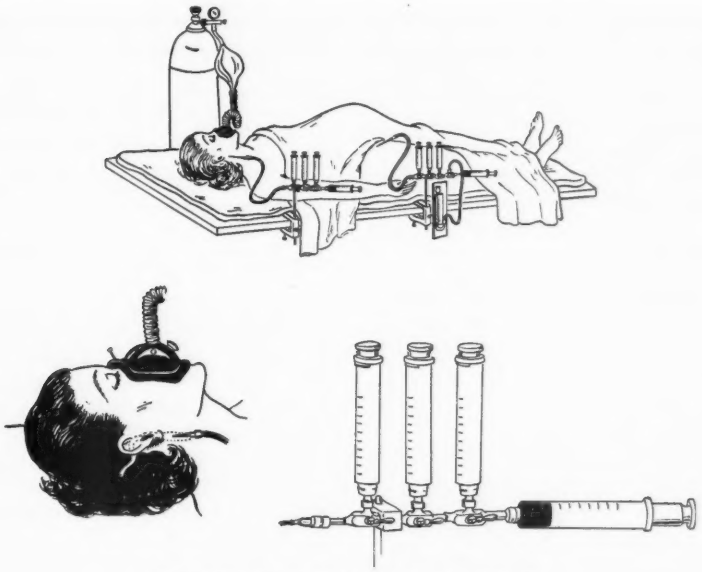

Fig. 2. Setup for cerebral blood flow determination.

lower. This is not surprising when it is recalled that it has been shown that there is normally an increased plasma volume at term (3, 5, 19, 23), the so called hydremia of pregnancy. Another factor frequently found in a group of unregistered patients who present themselves for the first time after a complication of pregnancy has developed is an abnormally lowered hemoglobin. This lessens the carrying power of the blood for oxygen and to a lesser extent for carbon dioxide. It is interesting that the arterial-venous oxygen differences $(A—V)_{O_2}$ were approximately the same showing that during pregnancy the brain has the ability to extract the usual amount of oxygen from the blood even though the blood coming to it carries less oxygen. Thus the oxygen content of the venous blood leaving the brain is even more depleted, it being 37 per cent less than in normal males.

The lowered nutritive index of the brain of 2.1 in pregnancy compared to 2.8 in males is highly significant. This emphasizes the fact that the brain in normal pregnancy is maintaining a normal oxygen utilization in the face of a diminished oxygen supply, the latter being the result of the relative anemia which occurs in this condition.

In the comparison between the two series of normals, the nutritive index is the only one of the major functions being studied which shows a significant difference. As seen in the table, the cerebral blood flow, the respiratory quotient, the cerebral metabolism of oxygen, and the cerebral vascular resistance give very similar values in the two groups.

TOXEMIAS OF PREGNANCY

After the establishment of normal values for pregnant women, 29 patients with toxemia of pregnancy were studied. Using the classification proposed by the American Committee of Maternal Health in 1939 there were 16 patients with hypertensive toxemia, 8 patients with pre-eclampsia, and 5 convulsive eclamptics.

Because of the importance of excluding all possible factors which might alter the cerebral state in toxic patients, an effort was made to perform the studies before any therapy whatever had been given. In order that treatment might not be delayed, the equipment necessary for the study was kept in

readiness at all times so that the investigation could be carried out immediately upon the patient's admission to the ward. Three of these tests were done between successive convulsions during coma. One had but one convulsion and was rational and conscious when the blood flow was performed. The only eclamptic who received any therapy before the tests were completed was still in a semicomatose state.

TABLE II.—THE MEAN ARTERIAL BLOOD PRESSURE (FEMORAL) IN MILLIMETERS OF MERCURY

	Millimeters of mercury
Normal pregnant women	90.5
Hypertensive toxemia	125
Pre-eclampsia	118
Eclampsia	124

Mean arterial blood pressure. These values were taken directly from the femoral artery. Table II shows the increased mean values of toxemia patients over normal pregnant women.

TABLE III.—CEREBRAL BLOOD FLOW

c.c. per 100 gm. brain/min.

$$CBF=\frac{100\ V_{10}\ S}{\int_0^{10}(A-V)\,dt}$$

Normal pregnant women	56
Hypertensive toxemia	55
Pre-eclampsia	54
Eclampsia	51

Cerebral blood flow. The flow of blood through the brain was found to be but little affected by the toxemias of pregnancy. The normal values obtained in the study of women afflicted with essential hypertension, in whom there was some degree of superimposed toxemia, bears out the work of Kety and his collaborators (10) on patients with essential hypertension per se that the blood flow is not affected by this condition. While the pre-eclamptics had comparatively normal blood flows, the patients with eclampsia showed a tendency toward lower values. While the flow of 51 cubic centimeters per 100 grams of brain per minute in eclampsia compared to the normal value of 56 cubic centimeters is not statistically significant in this study, it may approach significance in a larger group of cases.

TABLE IV.—THE CEREBRAL METABOLIC RATE IN TERMS OF OXYGEN

c.c. o_2 per 100 gm. of brain per minute

$$CMR_{O_2}=\frac{CBF}{100}\times(A-V)_{O_2}$$

Normal pregnant women	3.5
Hypertensive toxemia	3.4
Pre-eclampsia	3.4
Eclampsia	2.8

Cerebral metabolic rate in terms of oxygen. The cerebral utilization of oxygen in patients with pre-eclampsia and hypertensive toxemia is normal. In convulsive eclampsia, however, the rate of oxygen consumption per 100 grams of brain per minute is 2.8 cubic centimeters in comparison with 3.5 cubic centimeters in normal pregnancy. This difference approaches significance when the usual statistical methods are used.

TABLE V.—CEREBRAL VASCULAR RESISTANCE

mm. Hg per c.c. of blood per 100 grams brain per minute

$$CVR=\frac{\text{Mean arterial blood pressure}}{CBF}$$

Normal pregnant women	1.6
Hypertensive toxemia	2.3
Pre-eclampsia	2.0
Eclampsia	2.5

Cerebral vascular resistance. The pressure necessary to force 1 cubic centimeter of blood per minute through each 100 grams of brain is significantly increased in all toxemias of pregnancy. The highest resistance is seen in cases of eclampsia; in these patients a value of 2.5 is obtained in contrast to the normal of 1.6.

TABLE VI.—RESPIRATORY QUOTIENT OF THE BRAIN

$$RQ=\frac{(V-A)_{CO_2}}{(A-V)_{O_2}}$$

Normal pregnant women	0.98
Hypertensive toxemia	0.94
Pre-eclampsia	0.98
Eclampsia	1.06

Respiratory quotient of the brain. The RQ of the brain in normal human beings is approximately unity indicating that the brain utilizes carbohydrates almost exclusively as its source of energy. In normal pregnant

women, as well as in patients with toxemia of pregnancy, there is little deviation from this value.

TABLE VII.—ARTERIAL-VENOUS OXYGEN DIFFERENCES AND NUTRITIVE INDEX OF THE BRAIN

	$(A—V)O_2$	$\frac{AO_2}{(A—V)O_2}$
Normal pregnant women	6.5	2.1
Hypertensive toxemia	6.3	2.2
Pre-eclampsia	6.3	2.2
Eclampsia	5.5	2.8

Arterial-venous oxygen differences $(A—V)O_2$ (*Table VII*). The amount of oxygen extracted by the brain per 100 cubic centimeters of blood in toxemia is not significantly different from that in normal pregnant women. However, once again there is seen a tendency toward a difference in the eclamptic group which in a larger series of cases would become increasingly significant. The patients in this group of most severe toxemias used an average of 5.5 volumes per cent of oxygen whereas the patients in the normal group used 6.5 volumes per cent.

As shown earlier, the $CMRO_2$ (amount of oxygen consumed per 100 gm. of brain per minute) is lowered in eclampsia. This, of course, is the reason for the decrease in the arteriovenous oxygen difference.

The nutritive index of the brain (*Table VII*). The NI is approximately the same in pre-eclampsia and hypertensive toxemia as it is in the normal pregnant woman (2.1). In eclampsia there is a significant increase in this index to 2.8. This fact further emphasizes that the brain is not suffering from a lack of oxygen supply but rather from a failure to utilize the oxygen which is provided by the incoming arterial blood to a normal extent.

DISCUSSION

This study offers evidence that the physiology of the brain in normal pregnancy is much the same as that of normal young males. The only exception to this is a propensity of the brain to utilize approximately the same amount of oxygen as does the nonpregnant individual even though the arterial blood coming to it was shown to carry 26 per cent less oxygen. The decreased oxygen carrying power of the arterial blood of pregnancy is thought to be mainly due to the physiologic hydremia.

In the toxemias of pregnancy several pertinent facts appear to be evident from this investigation. It seems significant that, aside from a slight degree of reduction in eclampsia, the blood flow is found to be constantly normal. This fact assumes importance to us inasmuch as several theories concerning the causation of eclampsia postulate that there is a greatly reduced blood flow to the brain.

Stander, in his monograph on toxemia, states that Traube and Rosenstein in 1864 first proposed that edema and actual anemia of the brain are the etiological factors in the production of eclampsia. More recently Zangemeister postulated that the development of cerebral edema caused such an increased extravascular pressure that the blood supply to the brain was greatly diminished. This "hydrops gravidarum" concept explained that the cells of the brain were inadequately nourished due to this anemia bringing about cerebral irritation and convulsions. However, the present study reveals that cerebral blood flow is maintained at normal levels which points to the conclusion that the symptoms of eclampsia cannot be explained upon the basis of generalized cerebral ischemia.

The cerebral vascular resistance is the function affected most frequently in toxemia of pregnancy. We found essential hypertension upon which toxemia was superimposed similar to that in nonpregnant patients with essential hypertension in this respect. In pre-eclampsia the resistance was quite high, but the greatest degree of cerebral vascular resistance was encountered in the presence of eclampsia.

The mechanism of this abnormality is most likely based upon a narrowing of the vessels within the brain. This might be due either to an intrinsic action within the vessel itself such as vasospasm, or to an extrinsic pressure caused by edema or increased intracranial pressure of the cerebrospinal fluid. In essential hypertension these extrinsic factors are not observed as a rule, nor are they in pre-eclampsia although generalized edema is

more likely to develop. In eclampsia a wet brain is not an unusual finding at autopsy although there are many cases, especially the severe so-called "dry eclamptics" which do not exhibit this abnormality. In our experience, increased spinal fluid pressure is an inconstant finding. Therefore, while any of the three mechanisms may bring about the increased cerebral vascular resistance in eclampsia, it is likely that vasospasm is the most frequent cause.

It has been recently shown by Odell, Aragon, and Pottinger that there is an increase in the cohesiveness of red cells in toxemia of pregnancy. This has been called "sludging" by Knisely and brings about a slowing of blood flow through the smaller venules as observed in the conjunctiva. Whether or not such a phenomenon could increase the resistance to blood flow in the brain is problematical. If such takes place it might be postulated that there is an immediate reflex increase in blood pressure which maintains the cerebral blood flow at a normal level.

It has been shown that partial constriction of arterial inflow to various organs may cause vasospasm and hypertension. Cushing (1, 2) showed that restriction of the blood flow to the brain causes hypertension. The work of Goldblatt upon the kidney revealed a similar cause and effect as did the work of Ogden, Hildebrand, and Page upon partial constriction of the uterine arteries in pregnant dogs. While our study shows no interference with the blood flow to the brain during the disease, it is as yet conjectural as to whether or not there is a preliminary transient lessened blood flow to the brain, kidneys, or placenta which brings about the increase in blood pressure and vasospasm. A generalized capillary spasm over the body has been suggested by the work of Hinselmann, of Haselhorst, and of others.

Halbertsma, in 1884, postulated that a deficiency of oxygen is the immediate cause of eclampsia. Since then numerous writers have regarded a disturbance in oxidation as the exciting cause. Stander states, "Whatever theory ultimately explains the etiology of eclampsia will have to take decreased or deficient oxidation into account." In our tests the oxygen consumption of the brain was depressed in eclampsia but was not impaired in the nonconvulsive toxemias. This finding, therefore, seems to correlate to some extent with the mental clearness of the patient. The amount of oxygen carried in the arterial blood is approximately the same in all types of toxemia as it is in normal pregnancy. It is conceivable that the brain of the eclamptic has lost the ability to utilize oxygen as well. With cerebral blood flow unaltered to any significant degree, this points to the likelihood that there is some inherent disturbance in the brain cells themselves rendering them less capable of using oxygen.

It is hoped that this report will stimulate the further investigations which are necessary for a more complete understanding of the pathologic physiology of the brain in the presence of the toxemias of pregnancy.

SUMMARY

1. By a recently devised method, the cerebral blood flow and related circulatory and metabolic functions of the brain have been studied for the first time in normal pregnancy as well as in patients with toxemia of pregnancy.

2. Normal pregnant women were found to have a lowered oxygen content of the arterial blood but were able to show the same amount of oxygen utilization by the brain as were normal nonpregnant individuals whose arterial blood carried 26 per cent more oxygen.

3. The cerebral blood flow was found to be normal in all toxemias of pregnancy.

4. The cerebral vascular resistance was significantly increased in each type of toxemia, the greatest degree being present in eclampsia.

5. The oxygen consumption of the brain was significantly decreased in eclampsia but was not impaired in the nonconvulsive toxemias.

6. The possible implications of these findings are briefly discussed.

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STUDIES ON THE EFFECTS OF CONCOMITANT VENOUS LIGATION IN ACUTE ARTERIAL OCCLUSION

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SINCE Sir George Makins, on the basis of observations made during the Boer War, postulated the theory that concomitant vein ligation at the time of ligation of a major artery of an extremity lowered the incidence of gangrene, numerous contradictory clinical and experimental reports have been published on the subject.

Strong evidence in support of the theory was that of Brooks, Johnson, and Kirtley, who reported that the incidence of massive gangrene in the extremities of rabbits was 14.5 times as high when the common and external iliac arteries alone were ligated as when the common iliac vein was ligated simultaneously. This result was not corroborated in experiments by Wilson.

Other important evidence comes indirectly from the reports of clinical improvement in circulation produced by the use of intermittent venous occlusion in peripheral vascular disease. Linton and his associates demonstrated experimentally with the thermostromuhr that concomitant venous occlusion increased the volume of the blood flowing in a ligated artery.

In carrying out our experiment two projects were undertaken. The first was to repeat the simple and logical experiment of Brooks and his associates. The second was to seek a more sensitive test for determination of circulatory changes in the limb following ligations of major vessels.

METHODS

Repetition of the experiment of Brooks, Johnson, and Kirtley. Rabbits were used. Under nembutal anesthesia the right common iliac and external iliac arteries were ligated and divided through a transperitoneal incision. In another group of rabbits the right common iliac vein was ligated simultaneously with the arterial ligations. Repeated observations were made for 60 to 90 days, after which those animals which had survived were sacrificed and autopsies were performed whenever indicated.

With the exception of a single animal which died of an early massive gangrene about 36 hours postoperatively, we have excluded those animals which did not survive 48 hours postoperatively since rabbits are extremely sensitive to variable doses of anesthesia and to changes in climatic conditions. One hundred observations have been made—50 in each group.

The use of radioactive sodium in circulation studies—modification of the method of Smith and Quimby with dogs. With the dog lying on his back and each hind paw carefully strapped in place over the port in the lead shield covering the Geiger tube (Fig. 1), doses of 100 to 200 microcuries of radiosodium were injected into the jugular vein. Readings were taken continuously for 1 hour, alternating counts in each paw every minute. By this means relatively corresponding curves were obtained, representing the build-up of radiosodium ion concentration in the paws (Fig. 2). After normal controls had been established, the femoral vessels just below the inguinal ligaments were isolated under local anesthesia. Both superficial femoral arteries were ligated and divided, and the femoral vein on one side was ligated at the same level. Further doses of radioactive sodium were then injected into the jugular vein and similar readings taken immediately postoperatively and on the first and subsequent postoperative days. The total number of counts was charted, making necessary corrections for previous doses and

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This study is being carried further under a medical research contract with the United States Army.

TABLE I.—INCIDENCE OF COMPLICATIONS FOLLOWING LIGATION OF ILIAC VESSELS IN 100 RABBITS SURVIVING SURGERY 48 HOURS

	Artery only 50 rabbits per cent	Artery and vein 50 rabbits per cent
Massive gangrene	6	6
Focal necrosis	40	34
Contracture	36	22
Atrophy	60	36

changes in sensitivity of Geiger tubes. Figure 3 represents curves obtained in this manner. There were, however, wide individual variations.

This method has not proved entirely satisfactory for our purposes because relatively large doses of radiosodium are required; each reading is continued for an hour, and the curves obtained proved to be at best qualitative whereas we were in search of an exact quantitative measurement of blood flow.

The clearance method of Kety. This is based on the assumption that radioactive sodium is a freely diffusible ion and if injected locally into muscle its rate of disappearance from the injection site is an index of effective circulation in that region. A minute amount of sodium (5.0 to 10.0 microcuries in 0.1 c.c. of physiologic saline solution) was injected into the distal portion of the gastrocnemius muscle in the rabbits. The portion of the leg injected was strapped over the port of the Geiger tube, and continuous readings were taken for a period of 15 minutes. This series of counts produced an exponential curve which, when plotted on semilogarithmic paper, gave a straight line. From the incidence of fall of this line a constant (K) was calculated which we have used as an index of the blood flow in the injected muscle.

$$K = \frac{\log C_1 - \log C_2}{0.4343\,(t_2 - t_1)}$$

C_1 = counts per minute at first reading
C_2 = counts per minute at second reading
t_1 = time at first reading
t_2 = time at second reading
0.4343 = log e

This technique was applied to a series of rabbits in which ligation of vessels was performed as described in the first method. Curves obtained with this method were constant in shape and are illustrated in Figure 4.

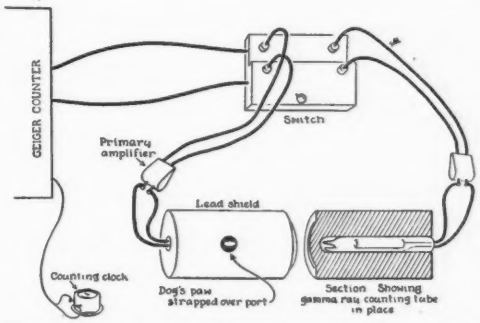

Fig. 1. The γ ray counting tubes are kept in 2 inch thick lead shields and are connected as shown to the Geiger-Mueller counter. The port in the shields is about the diameter of the Geiger tubes.

RESULTS

1. The tabulations in Table I show considerable disagreement with the observations reported by Brooks and his associates. Our incidence of early massive gangrene after common and external iliac artery ligation was only 6 per cent and was unaffected by simultaneous concomitant vein ligation. The most characteristic effect resulting from either of these procedures was the development of late focal necrosis beginning in the skin of the paw and often resulting in complete necrosis and separation of the entire paw. This effect occurred in 40 per cent of rabbits following arterial ligations alone and in 34 per cent of rabbits who had concomitant vein ligations. The difference is not statistically significant. There was a somewhat higher incidence of contractures (36 per cent compared to 22 per cent) when vein ligation was not performed.

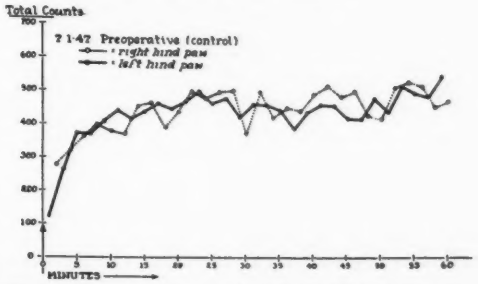

Fig. 2. Type of curve obtained in both hind paws of a normal dog, representing the build-up of radiosodium ion concentration after intravenous injection.

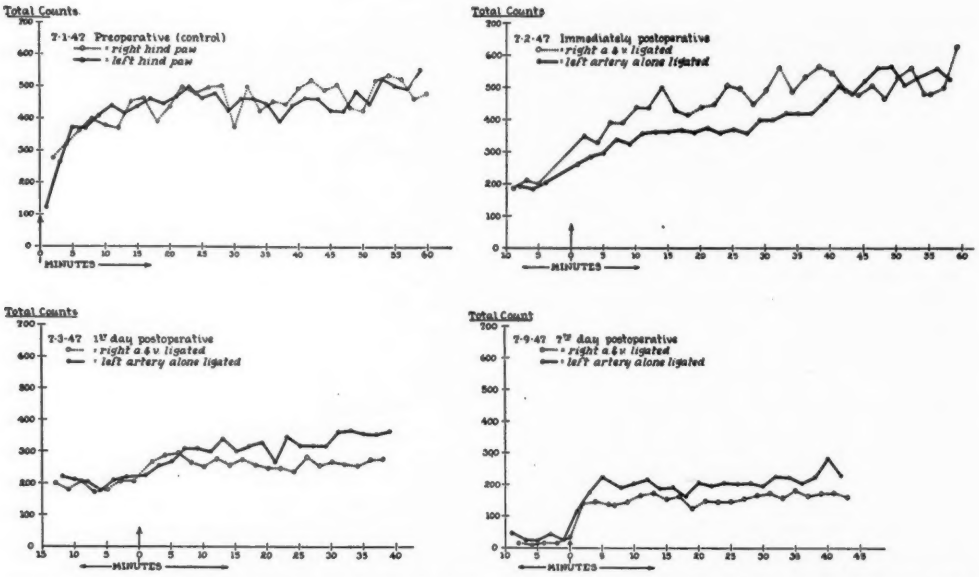

Fig. 3. Radioactive sodium build-up curves in the hind paws of a dog preoperatively and immediately and on the first and seventh days after ligation of the left femoral artery and the right femoral artery and vein. The left side showed a slower build-up rate immediately after ligation but a faster one on the first and seventh postoperative days. These results were not consistent in all animals.

2. Using the radioactive sodium technique of Smith and Quimby we have obtained no statistically significant records because of a lack of accurate quantitative measurements and because we were unable to obtain constantly reproducible curves.

3. The technique suggested to us by Kety yielded some most useful observations. By this method we have completed studies on 21 rabbits, some of which have been followed for over 2 months postoperatively. A number of others have been studied preoperatively and

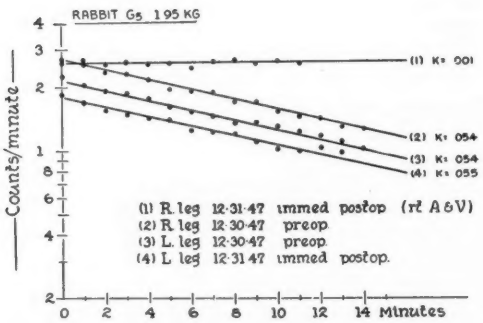
RABBIT G5 1.95 KG
Counts/minute
(1) K= 001
(2) K= 054
(3) K= 054
(4) K= 055
(1) R. leg 12-31-47 immed postop (rt A & V)
(2) R. leg 12-30-47 preop
(3) L. leg 12-30-47 preop
(4) L. leg 12-31-47 immed postop.
Minutes

Fig. 4. Curves obtained semilogarithmically after injecting radiosodium into the gastrocnemius muscles of a rabbit before and after ligation of the right iliac arteries and veins and measuring the rate of radiosodium clearance. The results which are shown in these curves are constantly reproducible.

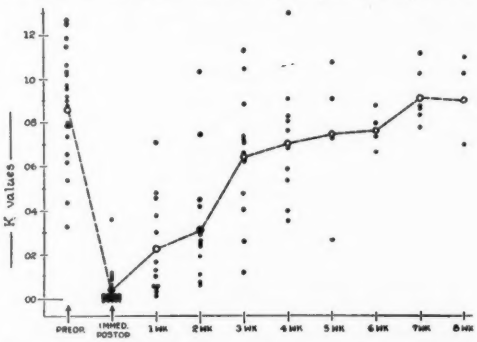

Fig. 5. The K values obtained in week by week recordings of radiosodium clearance in 21 rabbits, including 12 arterial and 9 arterial and venous ligations. A mean line is drawn to demonstrate the fact that the same general trend occurred in all animals; i.e., an immediative postoperative drop and then a gradual return to preoperative levels.

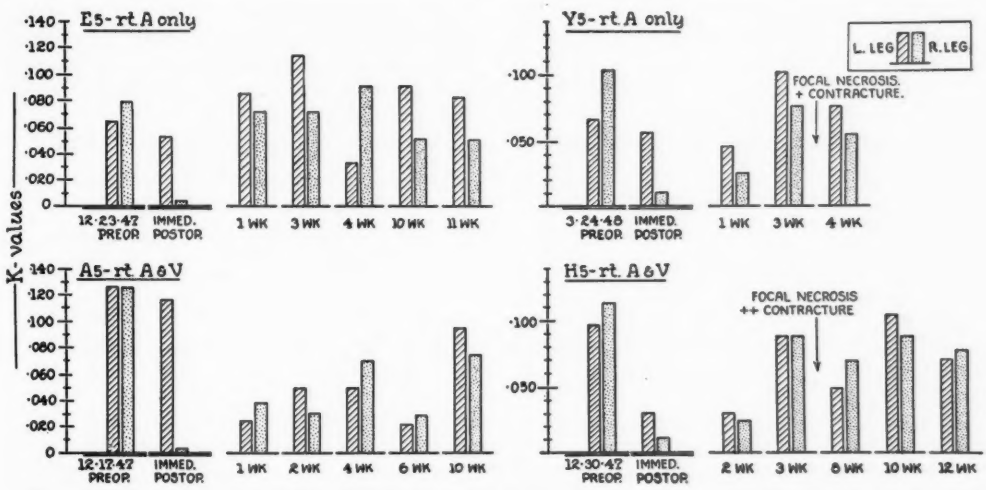

Fig. 6. Demonstration in 4 rabbits showing that the rate of radiosodium clearance from the gastrocnemius muscle drops immediately after iliac arterial (or concomitant venous or both iliac arterial and concomitant venous) ligation and gradually returns to near preoperative levels.

immediately postoperatively, but for various reasons (lack of a constant sodium supply, anesthetic deaths, etc.) have not been followed sufficiently long to be included. However, the records that are not included because they lack completeness have conformed to the pattern of those shown (Fig. 5, all K's; Fig. 6, E5–A5, Y5–H5).

In Figure 5 are plotted the K values in these 21 animals week by week. Twelve arterial and 9 arterial and venous ligations are included here. Of this group 7 animals developed focal necrosis or contracture, 4 occurring in the combined ligation group and 3 in the arterial ligation group. The circulation in the gastrocnemius muscle of all of the animals determined in this way, regardless of which operative procedure was employed and regardless of the presence or absence of gross necrosis or contracture in the limb, followed the same general trend. There is an immediate postoperative drop in the circulation in the gastrocnemius muscle followed by a return to close to the preoperative flow during the next few weeks.

A simpler demonstration of this trend is given in Figure 6 representing 4 of the experiments. Two of each group are shown, and 1 of each group developed focal necrosis. In all 4 the immediate postoperative drop occurred, followed by recovery to near preoperative levels.

Thus, we have observed that the circulation in the gastrocnemius muscle of the rabbit as determined by this method does not reveal what is occurring in the structures of the paw distal to it. Concomitant vein ligation has no effect on the clearance of radioactive sodium from the gastrocnemius.

DISCUSSION

The single striking feature in these experiments and in similar experiments of others is a serious lack of precise information about the peripheral circulation in the various component structures of the body. In an extremity which has been deprived of its major blood supply there have been few accurate measurements of blood flow in the skin, fascia, muscle, and bone. Thus, in these experiments, determination of blood flow in the gastrocnemius muscle gives inadequate indication of what is about to happen or has already happened to the paw just distal to it. Such fundamental phenomena require further investigation if we are to handle peripheral

vascular diseases and injuries on anything other than an empirical basis.

The use of radioactive sodium, especially in the manner described by Kety, is proving to be most helpful in these problems. Perhaps intradermal sodium injections may help to give more information on the problem although technical difficulties made its use impractical in these experiments.

CONCLUSION

We have been unable to determine that any benefit accrues from concomitant venous ligation in acute arterial occlusion. The evidence of Brooks and his associates in support of this theory has not been confirmed. Studies of intramuscular circulation by use of radioactive sodium fail to show any improvement resulting from this procedure.

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THYROGLOSSAL TRACT ABNORMALITIES— CYSTS AND FISTULAS

Report of 105 Cases from the Johns Hopkins Hospital Observed during the Years 1926 to 1946

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THYROGLOSSAL cysts and fistulas arise from epithelial rests in the remnants of the thyroglossal duct produced by the descent of the thyroid anlage. A brief review of the embryology shows that the thyroid anlage has its beginning as a diverticulum (i.e., evagination) from the floor of the pharynx, midway between the first and second pharyngeal grooves. Early in development, this anlage becomes a hollow stalked structure, known as the thyroglossal duct (23). This stalk usually loses its lumen to become a solid cord of epithelial tissue with its caudad, or pharyngeal end being marked by the foramen cecum at the base of the tongue. In the development of the embryo, the tongue forms at a later date than the thyroid anlage and the termination of the thyroglossal duct is buried within its substance. As a result of similar later development of the hyoid bone, the tract passes either anteriorly or posteriorly or through the hyoid. Caudal progression of the tract continues in the median line of the neck to a point below the thyroid cartilage where it terminates in the pyramidal lobe of the thyroid gland. Normally the epithelial lining of the tract undergoes degeneration and disappears (7, 12). When degeneration fails to take place, cysts or fistulas may occur anywhere along the course between the foramen cecum and the suprasternal notch. These cysts and fistulas are found either in the midline or slightly to one side. The drawings (Figs. 1 and 2) illustrate where these lesions may occur, as determined by this series of cases.

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Histologically, the cyst or fistulous tract may be lined by stratified squamous, columnar, or transitional epithelium (Fig. 3). After infection of the cyst or fistula, a heavy layer of fibrous connective tissue surrounds the tract. Lymphoid tissue, as seen in branchial cleft cysts and fistulas, is not observed in thyroglossal tract abnormalities (14). It has been reported that cancer may develop in the cyst wall or fistulous tract (7, 16). However, we have observed no neoplastic growths (23) in this present series.

Of the 105 cases seen in the Johns Hopkins Hospital, between 1926 and 1946, in 60 per cent the cysts or fistulas occurred between birth and the age of 10 years. The sex incidence was about equal for males and females there being 56 males and 49 females. These anomalies were noted in both white and colored patients: 70 cases were of the white race, and 35 of the colored race. In this series were seen: all possible locations of the abnormality which have been reported: intratongue (4) (Fig. 1, *A* and *B*), submental region (12), suprahyoid (11), at the level of the hyoid (12), infrahyoid (52), suprasternal (13); in the midline (19), to the right of the midline (13), and to the left of the midline (13). These locations are clinical, as noted in the hospital records and do not conform accurately to the anatomical locations of Figure 1. Too great an importance on these latter 2 figures cannot be stressed, since it is generally taught in the surgical text of today that thyroglossal tract abnormalities occur exactly in the midline (10, 12), and thus a great deal of confusion may be encountered.

Thyroglossal tract abnormalities are important, because they may be, and often are,

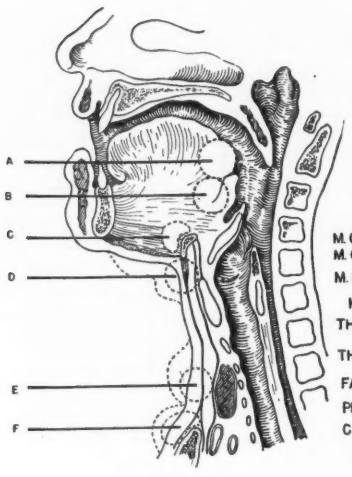

Fig. 1.

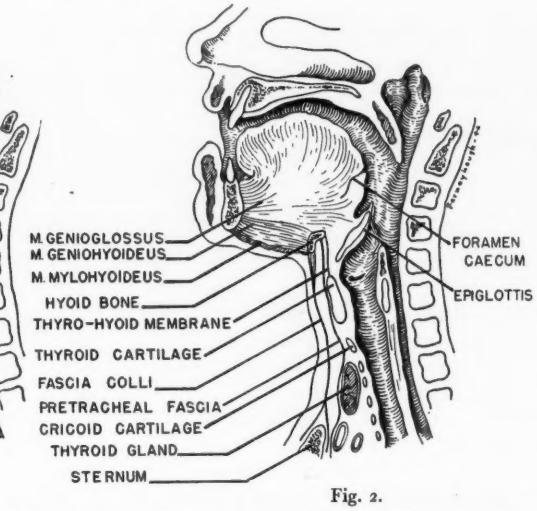

Fig. 2.

Fig. 1. Illustrates various locations of remnants of the thyroglossal tract. A, in front of foramen cecum; B, at foramen cecum; C, suprahyoid; D, infrahyoid; E, area of thyroid gland; and F, suprasternal.
Fig. 2. Drawing of sagittal section of neck. (Illustrations, Fig. 1 and Fig. 2, from *Tumors of the Head and Neck* by Ward and Hendrick).

the seat of recurrent inflammatory disease and are a cause of cosmetic disfigurement. Infection occurring in these cysts is often the first direct symptom which causes the patient to seek medical aid. Recurrent infection was noted in 52 cases in this present series, which was extensive enough in 15 to cause spontaneous rupture of the cyst. Marked infection was present in 10 patients admitted to the hospital, and extensive cellulitis was present in 3, producing what is commonly termed "bull neck." In 6 of the 10 patients, the only treatment warranted after admission was incision and drainage. However, all of these 6 patients were subsequently readmitted for radical surgical procedure with complete elimination of the epithelial tract. The cyst can vary in size from several millimeters to 6 or 7 centimeters in diameter (Fig. 4). A cyst located within the substance of the tongue usually presents the most alarming symptoms to the patient; such as, dysphasia, dysarthria, and choking sensations. Frequently, as cysts in the substance of the tongue or in the submental or suprahyoid area become larger, the patient notices tenseness in the tissues and also mild choking attacks.

The contents of the cyst is of a mucoid nature unless infection makes it purulent. Frequently, following infection, there is a rapid increase in the size of the cyst with pain and tenderness, and the cyst walls become thickened. Occasionally, there is a direct communication between the cyst and the foramen cecum; a thyroglossal tract sinus. In such a circumstance, pressure on the cyst will express fluid through the foramen cecum, thus clearly demonstrating a pharyngeal communication; present in only 2 of our cases. When infection occurs and progresses to suppuration with spontaneous rupture of the cyst, or if a cyst has been lanced, a sinus tract results. In this series, 34 per cent of the cases developed sinus tracts. Incision and drainage of a non-infected cyst, under any circumstances, is to be condemned.

In this series, admission examination revealed a cyst in evidence in 62 patients, or 59 per cent, a sinus tract in 36, or 34 per cent, and a palpable subcutaneous duct in 20, or 19 per cent. The term sinus tract is used to designate a discharging sinus in which the patient previously had a cyst which was lanced or became infected and suppurated (Fig. 5). A

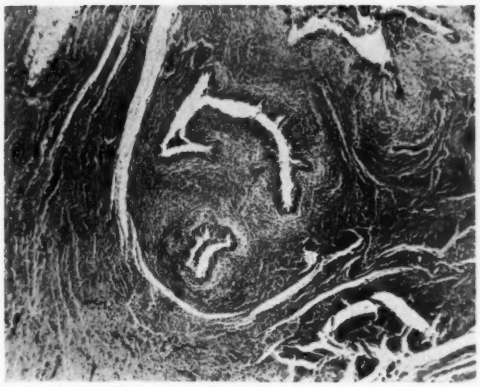

Fig. 3. A sinus tract lined with squamous epithelium surrounded by dense fibrous tissue. There is an infiltration with lymphocytes, plasma cells, fibroblasts, and a few polymorphonuclear leucocytes. Striated muscle is also present.

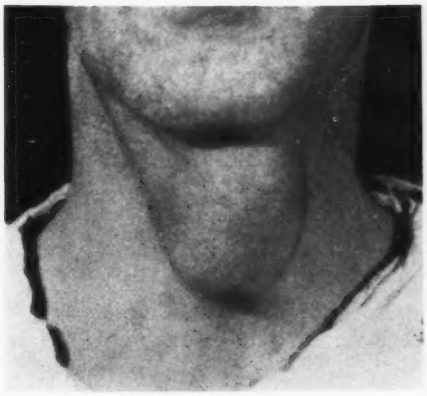

Fig. 4. Typical example of a thyroglossal cyst located in the infrahyoid region.

definite cord of tissue palpated under the skin is termed "a congenital duct." Of the 20 cases reported, 6 were present without evidence of cysts. Of these 6 cases, 4 were incidental findings in the examination for another medical disorder, and the remaining 2 sought medical advice for an actual infection of the duct tract.

Of the 62 patients who presented a cyst when examined, 47, or 76 per cent, were midline lesions, and 15, or 24 per cent, were lateral to the midline. In this group of patients, 53, or 85 per cent, had cysts below the hyoid bone. There were 28 lesions above the hyoid bone; 9, or 33 per cent, were cysts, while 5, or 16 per cent, were sinuses, and the remaining 51 per cent presented combined lesions. When the 77 cases located below the hyoid were analyzed, 53, or 68 per cent, were cysts, 24, or 31 per cent, were sinuses, and the remaining 7, or 1 per cent, were combined lesions.

In making the diagnosis of thyroglossal tract cyst or fistula, it is to be remembered that the cyst or fistula may occur any place from the base of the tongue (foramen cecum) to the suprasternal notch, and that these abnormalities are the most frequent cysts or fistulas occurring in that area. Occasionally, as mentioned, they may occur just to the right or the left of the midline, but this deviation is not far enough to cause any difficulty in the differential diagnosis. One of our cases was located within the substance of the tongue above the foramen cecum (Fig. 6). At examination, these cysts were smooth, ovoid or round, and translucent when examined with a transmitted light.

These cysts must be differentiated from a dermoid tumor, lipoma, sebaceous cyst, or from an enlargement of the pyramidal lobe of the thyroid gland, and enlarged lymphatic glands of the cricothyroid membrane. It was found that some of the cysts and fistulas were very superficially located, while others were quite deep. At operation, the lesions were found just beneath the skin, beneath the platysma muscle, beneath Colles' fascia, and still others beneath the pretrachial fascia. At examination, the tumor can usually be described as being cystic or fluctuant, but in 10 of these cases, the cyst was so tense that its cystic nature was overlooked and it was not until operation that the tentative diagnosis of a solid tumor was disproved. The cyst moved up and down with deglutition, and in the majority of cases movement of the cyst can be associated with movement of the hyoid bone. This was true in approximately 85 per cent of our cases.

Varying amounts of thyroid tissue may be found within the cystic mass or associated closely with it. This condition was present in 6 of our cases. It was noted in a 14 year old male who had a cyst measuring about 4 by 4

Fig. 5. Thyroglossal sinus which resulted from the repeated incision of a cyst over a period of 20 years.

centimeters in size that was within the substance of the tongue, anterior and above the foramen cecum. This patient had symptoms of a cyst for 11 years previous to admission to the hospital. The cyst was removed by local intraoral excision, and approximately 4 or 5 months following the operation, the patient developed symptoms of hypothyroidism, almost to the stage of cretinism. There was no palpable thyroid gland in the neck. This patient has been followed for a period of 21 years postoperatively, during which time it was necessary for him to continue taking thyroid extract regularly. At the present time he is completing a college education and is normal in every respect (Fig. 6).

Thyroglossal tract fistulas or sinuses should not be confused with any other sinus tract. The opening of a branchial fistula or sinus tract is on the side of the neck and not "just to the right or left of the midline." Either fistulous tract may communicate with the oral cavity. If a thyroglossal tract fistula or sinus communicates with the oral cavity, it does so always at the foramen cecum, whereas, branchial cleft fistulas or sinuses open at Rosenmueller's pouch in the lateral pharyngeal wall. If there is any doubt of the extent of the fistulous tract or sinus, it may be injected with a radio-opaque substance and a roentgenogram made. This injection is usually very painful and should be done only when necessary. However, if it is desired to visualize the fistulous tract with lipiodol for diagnosis, the external opening may be injected with a local anesthesia, a small catheter or lacrimal duct syringe passed just within the opening and 2 or 3 cubic centimeters of warm lipiodol solution injected.

TREATMENT

The treatment of thyroglossal tract abnormalities is entirely surgical excision of all the epithelial tissue. The authors would again like to stress the inadvisability of ever lancing a thyroglossal duct cyst unless it is infected and shows evidence of suppuration. Simple incision of the cyst serves no useful purpose, but does create a persistent draining sinus that is constantly discharging mucus and is very prone to become infected. In this series, in 21 cases the cysts had been lanced previous to the time the patients sought medical aid at the Johns Hopkins Hospital. All of these patients had very unsightly scars, and 18 had persistently draining sinuses. The election to incise and drain one of these cysts should rest on sound surgical judgment, such as would be used in determining when to open and drain any localized, fluctuant, obviously grossly infected lesion.

The injection of a sclerosing solution should never be used under any circumstances. The injected solution cannot be depended upon to reach all the minute epithelium-lined side pockets of the abnormality. Irradiation therapy, also, should not be used, since these lesions are not radiosensitive and the application of radium and x-ray serves only to complicate subsequent surgical procedures. One patient in this series was treated with radium which resulted in the destruction of so much skin that multiple plastic procedures were necessary to close the defect (Fig. 7).

Gross and Connerley state that operative intervention for this disorder is not necessary

Fig. 6. Patient with thyroglossal duct cyst located above the foramen cecum.

in every case. However, we feel that by far the majority of these lesions will eventually become infected, and thus should be removed. In these cases, 54 (51%) gave a history of infection at some time during their course. Of these, 25 had gross infection when they sought aid at the Johns Hopkins Hospital. Certainly operative excision should be advised for all sinuses because of the high probability of recurring infection (Fig. 5).

Regardless of the operative approach that is adopted for this condition, it is extremely necessary that the entire epithelial tract of the cyst, sinus, or fistula be completely removed. Forty-three of the patients in this group had a history of having had one or more surgical procedures previous to admission to the Johns Hopkins Hospital. Twenty-one patients gave a history of having had the cyst lanced, and 22 had local excisions of the abnormality.

Endotrachial anesthesia is the anesthesia of choice in removing these abnormalities.

The operative procedure outlined by Sistrunk (20, 21) in 1920 is the best basic procedure for radical removal of thyroglossal duct abnormalities (23). The authors believe that if the Sistrunk technique is carefully followed with a few modifications, there will be a minimal number of recurrences. It must be stressed that a midline vertical incision is contraindicated, as it does not give sufficient exposure and inevitably results in an unsightly midline contraction, which requires plastic procedures to correct. In following Sistrunk's principles, a transverse incision 5 to 8 centimeters in

Fig. 7. Ugly scar after injudicious and repeated x-ray treatment of a thyroglossal cyst.

length is made over the cyst, if a cyst is present, or an elliptical transverse incision around the opening of a sinus or fistula (Fig. 8). The skin, subcutaneous tissue, and platysma muscle are reflected. The cyst or fistulous tract is followed to the level of the hyoid bone. At this point it will be noted that the longer fibers of the ribbon muscles, the sternohyoid come into view. At the junction of these 2 muscles, the hyoid bone can readily be palpated. Again it should be stated that the fistulous tract can be anterior, posterior, or pass through the hyoid bone. In order to insure complete removal and to facilitate exposure above this point, the central portion of the hyoid bone is freed above and below, and 1 centimeter of the hyoid directly adjacent to the fistulous tract is removed with a generous block of tissue well around the sinus or fistulous tract. To facilitate the removal of a portion of the hyoid bone, the hyoid is grasped with forceps just to one side of the proposed site of resection. The bone is pulled forward and the center is removed with scis-

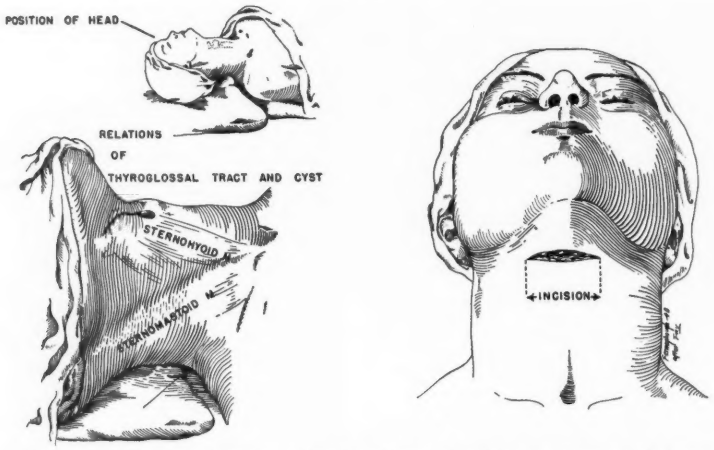

Fig. 8. Illustrations of position of head and type of incision for removal of thyroglossal tract abnormalities in the upper neck. A similar type of incision is used for thyroglossal abnormalities in the lower part of the neck. (Redrawn from Sistrunk.)

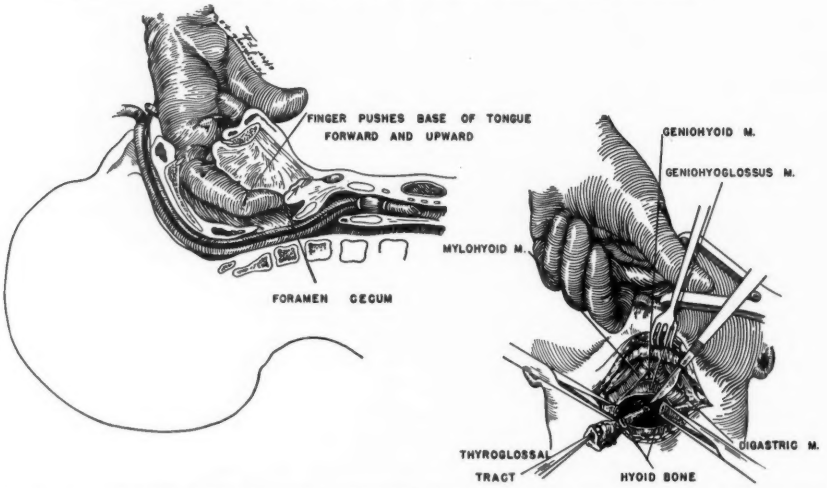

Fig. 9. Endotracheal tube in place. Assistant's finger in the mouth forces base of tongue and foramen cecum forward facilitating coring out stalk of tract. (Modified and redrawn from Sistrunk.)

sors if the patient is under 4 years of age, or cut with bone cutters in older patients. Tension on the fistulous tract will pull forward the centrally freed portion of the hyoid bone (Fig. 9). Frequently the tract above the hyoid is very small and pliable and care must be exercised to prevent tearing it. An assistant's finger placed in the mouth, exerting pressure against the base of the tongue, forcing it forward, greatly facilitates removal of a core of tissue, including the muscles around the stalk of the tract right up to the foramen cecum. The fainthearted will usually hesitate to follow this procedure, as he fears entering the mouth or the pharynx. However, in following this technique the tract may be followed to the base of the tongue and there removed with no untoward effects. Usually a

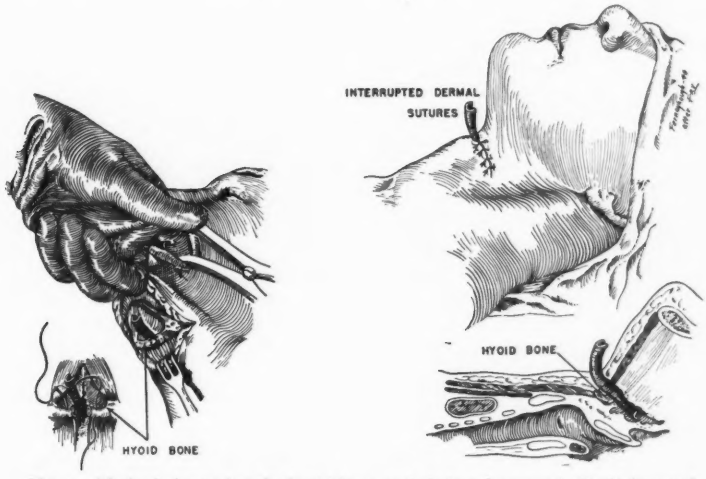

Fig. 10. Method of suturing the hyoid bone and closing the wound. Drain inserted. (Redrawn from Sistrunk.)

single pursestring suture of fine chromic catgut, carried on a round needle, will close the defect at the foramen cecum, inverting the mucosa into the mouth. The musculature of the tongue is brought together in the midline with interrupted sutures of fine silk or fine chromic catgut. The severed edges of the hyoid bone are brought together with catgut sutures placed directly through the bone, if the patient is in the younger age group; otherwise, the sutures are placed through the periosteum. It is not even necessary to approximate the edges of the hyoid. Such a defect will not result in any derangement of the action of the local muscles. A small rubber dam drain or tiny tube is placed deep in the muscles of the tongue to facilitate immediate postoperative drainage, and the skin edges are approximated with subcuticular and end-on mattress sutures of fine silk (Fig. 10). Removing these skin sutures in a minimum of 4 days and a maximum of 5 days results in a fine hairline plastic scar, practically invisible after a few months, particularly if the patient is quite young.

When a sinus tract is present, the authors do not think it worthwhile to inject it with methylene blue or other dye to outline its course, as the dye frequently spills and stains the surrounding tissues. However, if the operator desires to use a dye, it should be injected some 10 or 12 hours preoperatively to allow the dye to become fixed to the tissues of the sinus tract. Then, at operation, even if there is spillage into surrounding tissues, the sinus tract itself will be more deeply stained. However, any fistulous tract can be followed sufficiently without the aid of one of the dyes.

The 4 intratongue lesions in the series were all excised intraorally. None of these recurred.

RESULTS

Of the 105 cases studied, all were followed for a year or more. Seventy-eight, or 75 per cent, were followed for 5 years or more. The following statistics were based on the total 105 cases:

In the 28 suprahyoid lesions, it was not felt necessary to remove an area of the hyoid bone, but the lesion was followed to the foramen cecum in each case and a core of tissue was removed well around it. None of these lesions recurred, a cure rate of 100 per cent.

Of the 77 which occurred at or below the hyoid bone, 34 had an adequate section of the bone removed; 2, or 6 per cent, recurred.

In 43 of the 77 at or below the hyoid, no bone was removed and 11, or 25.6 per cent, recurred. These figures are evidence enough

to prove the value of removal of the central portion of the hyoid bone in order to follow the tract to the foramen cecum.

There were 13 recurrences in the entire series. In all but 2 of these cases, no hyoid bone was taken in the first operation. In these 2 cases, the authors feel insufficient bone was taken. In one of the cases, several small bits of hyoid were rongeured away, and in the other, the hyoid was touched with carbolic acid; both procedures to be condemned. In the reoperative cases, an adequate amount of hyoid bone was taken at the second operation. These reoperative cases have been followed from 1 to 15 years. In none were there recurrences following the second operation. In this series there were no operative deaths. One patient, mentioned before developed hypothyroidism 4 months after operation following the removal of an intralingual cyst, the wall of which contained the only thyroid tissue in the body. As mentioned before, 6 patients presented themselves with serious acute infection and were preliminarily treated by simple incision and drainage. Eight of the cases, after pathological study, revealed aberrant thyroid tissue within the wall of the cyst. In 6 of these cases, this aberrant tissue was embryological in structure.

CONCLUSION

Failures in this series, as well as in other reported series, are due to the inexperienced operator seldom appreciating the fact that it is necessary that thyroglossal tract abnormalities be followed to the foramen cecum at the base of the tongue, and that it is necessary in all instances to insure complete removal of all epithelial remnants, and in all lesions at the level of the hyoid bone or below to take 1 centimeter of the central portion of the hyoid bone and a block of tissue well around the sinus or fistulous tract. There are undoubtedly some few cases in which an incomplete procedure will result in a permanent cure, but this can be due to the chance that no epithelium lies within or near the hyoid bone. Simple dissection of the cyst, combined with simple ligation of the thyroglossal pedicle, and the treatment of thyroglossal fistula by means of scraping and cauterizing, the injection of sclerosing solutions, lancing the cyst, and treating the abnormality with x-ray or radium, give unsatisfactory results, serve only to increase the incidence of recurrence, and should be discarded (23).

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ERADICATION OF BENIGN LYTIC BONE TUMORS AND IMMEDIATE RECONSTRUCTIVE SURGERY WITH EMPHASIS ON BENIGN GIANT CELL TUMORS

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A STUDY of benign lytic lesions of bone still attracts considerable attention because of the confusion in the diagnosis and methods of treatment.

The etiology of benign giant cell tumor, localized osteitis fibrosa cystica, osteoid osteoma, and eosinophilic granuloma is not known but it appears to be directly concerned with an interference of blood supply, and trauma is a very likely contributing factor. Some writers consider these lesions as essentially inflammatory, others speak for the neoplastic theory. Codman thought that benign giant cell tumor represented a process of repair following rupture of a nutrient artery. The theory of the embryological basis for enchondromas is well known.

Bergstrand in writing on the genesis of giant cell tumor states that this condition is neither a tumor nor an inflammation but rather a process intimately associated with normal bone formation and resorption (Haggquoist-Hansen theory). He states that while he does not know the genesis he regards the condition as due to local bone resorption and based his opinion on the similarity of giant cell tumor to osteitis fibrosa cystica. While the cause is not known, certain observations favor assumption of the primary cause as due to disturbed circulation.

Decalcification and resorption of collagenous materials in the bone sets free the original bone forming tissue. Bone corpuscles approach each other and by fusion and nuclear division form giant cells. These form a syncytium lining the lumina of vessels, thus differentiating a fibrous bone marrow which replaces resorbed bone substance, proliferates and displaces true bone marrow, a reversion of bone tissue to primitive fetal type. This tendency to proliferation gradually ceases, giant cells disappear, and regression occurs. The ultimate result is a bone cyst surrounded by new bone tissue.

Eosinophilic granuloma of bone is a destructive lesion in which hystiocytes form the basic component of the lesion interspersed with varying numbers of eosinophilic leucocytes. Lichtenstein and Jaffe (26) were the first to describe this condition and give it its name. Green and Farber (16) were the first to show the relationship of this condition to that of Letterer-Sewes disease and that of Hand-Schueller Christian disease. Farber and Mallory believe that all these conditions are different expressions of the same basic disorder.

Osteoid osteoma was first described as a clinical entity by Jaffe (23) who believes that it is of neoplastic origin while other authors such as Brailsford believe it is inflammatory in origin. Ponseti and C. K. Barta describing the pathological picture bring out the fact that the typical histological appearance, the lack of inflammatory cells, and the negative smear and culture would indicate its neoplastic origin; however clinically and roentgenographically it appears to be a lesion of inflammatory origin.

Inclan believes that characteristics of giant cell tumor are more truly those of benign tumor rather than those of chronic inflammation, chronic irritation, or traumatic subcortical hemorrhage in cancellous bone.

Ernest E. Aegerter states that the giant cells found in such tumors as giant cell tumor of bone, giant cell tumor of tendons, osteogenic sarcoma, fibrous dysplasia (hyperparathyroidism), unicameral cyst, osteoid osteoma, eosinophilic granuloma and allied reticu-

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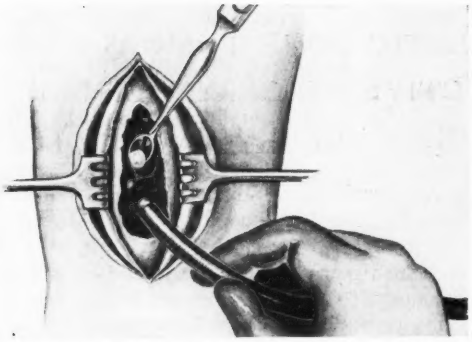


Fig. 1. Curettage and suction in removal of giant cell tumor.

loendothelioses, nonosteogenic fibroma and ossifying fibroma are all generically and functionally related, produced by the fusion of fibroblastic tumor cells for the purpose of phagocytosis. He states further that "the behavior of the tumor can be predicted only by the consideration of the cells of the fibrous matrix and that the giant cells give little or no clue as to whether the tumor will recur or metastasize. Fibrous matrix cells are found also in a number of bone lesions, both neoplastic and non-neoplastic. Many diagnoses of giant cell tumor of bone are based on these two criteria alone which is a mistake. The terminology would be self-explanatory and classification simplified if fibromas of bone were called giant cell fibroma, nonosteogenic fibroma and ossifying fibroma."

The lytic lesions of fibrous dysplasia of bone, osteitis fibrosa cystica generalisata, or von Recklinghausen's disease, present a picture which may very easily be confused with metastatic carcinoma. The etiology of these lesions is definitely known as an adenoma of a parathyroid gland. The diagnosis is made from a careful history, absence of a primary lesion, hypercalcinuria, hypercalcemia, hypophosphatemia, and renal calcinosis.

The purpose of this presentation is not to review the details of the various etiological theories, nor to delve at length into the pathological findings of these lesions, which are so well described in numerous writings, but rather to discuss the methods of treatment and to suggest some refinements in technique.

The diagnosis of giant cell tumor is made by the complaints of localized pain, swelling, impaired function, and a crackling or give sensation. The usual location is at the end of certain long bones, especially the distal end of the femur, the proximal end of the tibia, proximal end of the fibula, the distal end of the radius, and the proximal end of the humerus. Other bones including the vertebrae are frequently involved. The roentgenogram is often diagnostic, showing widening, rarefaction, and

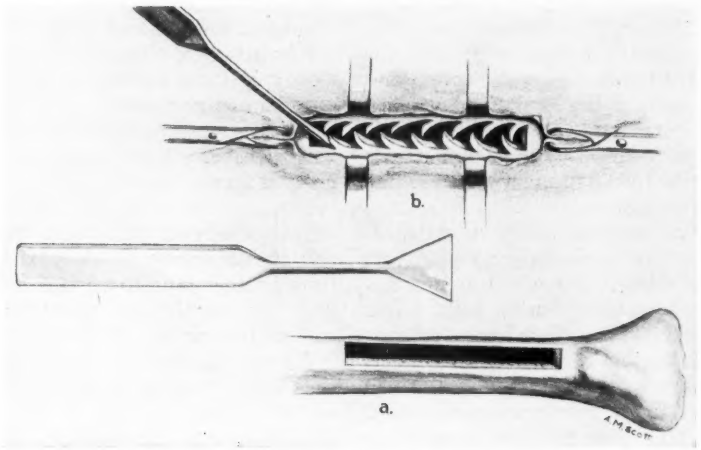
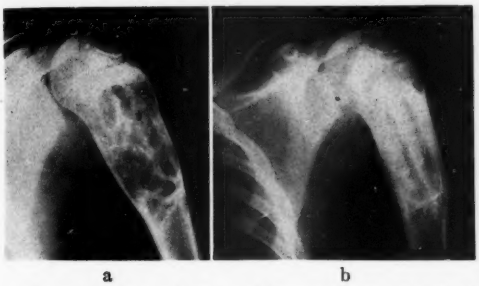


Fig. 2. To stimulate regeneration. Multiple pedicle chip grafts after removal of massive graft.



a b

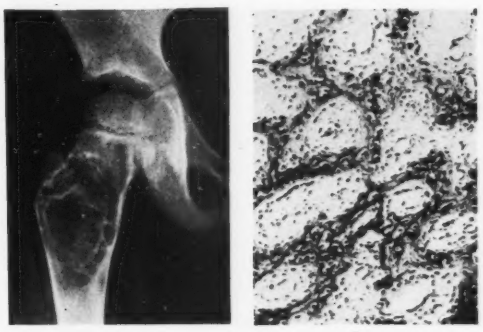
Fig. 3. Case 1. A. K., 10½ years of age. Localized osteitis fibrosa cystica. a, Before surgery; b, 5 months after surgery, curettage, aspiration, tibial grafts (struts and chips).

occasional trabeculation of the medulla, with thinning and bulging of the cortex.

Grout discusses the difficulties of roentgenological interpretation and misunderstandings which are liable to occur if too much stress is placed on roentgenographic features without reference to clinical findings and other means of investigation. He believes that it is not scientific to state that roentgenographic features alone are sufficient to establish the nature of any bone tumor. He shows series of roentgenograms of sunray appearance considered to be typical of osteogenic sarcoma which in each case showed a different pathological condition. The same situation was present with various osteolytic lesions.

Brailsford states that it is very important to correlate the clinical, roentgenological, and histological findings before radical surgery such as amputation is performed. He cites a number of cases showing roentgenograms typical of osteogenic sarcoma which proved to be benign. He also presents a case in which, although the clinical findings did not substantiate the diagnosis of a Ewing's sarcoma, the roentgenogram suggested and the biopsy revealed a highly malignant Ewing's tumor. The patient refused surgery. The lesion completely resolved and 10 years after she is still fit and well.

The treatment of benign giant cell tumors, localized osteitis fibrosa cystica, enchondroma, osteoid osteoma and eosinophilic granuloma and some others of the benign lytic bone lesions, seems to vary, depending to some extent upon the specialty of the attending physician,



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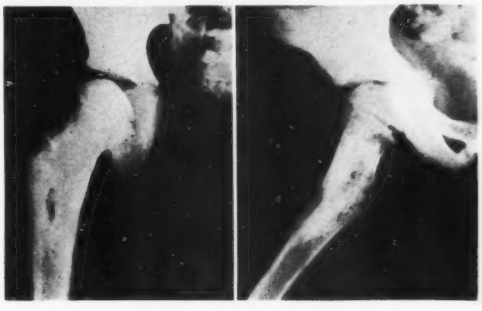


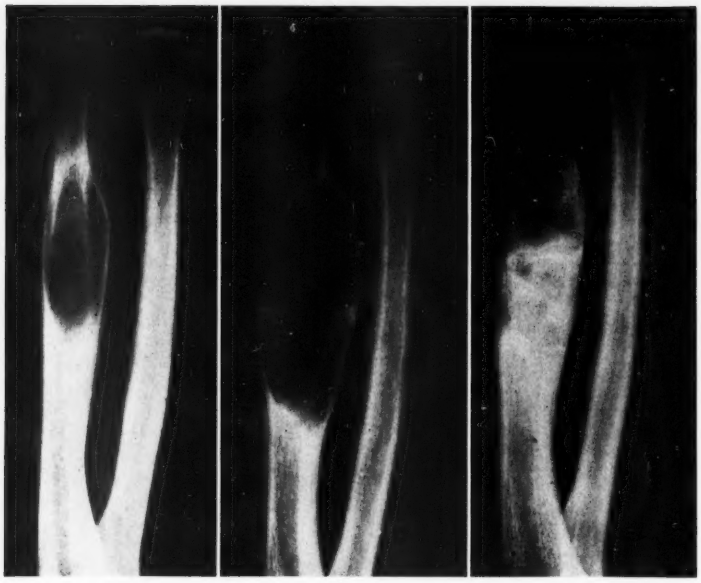
c

Fig. 4. Case 2. N. O'B., 4 years of age. Localized osteitis fibrosa cystica. a, Before surgery; b, microscopic section showing the marrow space diffusely replaced by young connective tissue cells with a number of blood vessels; there is no evidence of malignancy; c, anteroposterior and lateral views showing gradual reossification of the involved area, 13 months after surgery.

the radiologists favoring irradiation and the surgeons, resection, while a few clinicians favor both. Of the latter group, some speak for preoperative irradiation and others suggest postoperative therapy, and one surgeon gives his patients with giant cell tumors irradiation before and after surgery.

Badgley, discussing the presentation of Meyerding, states that a combination of roentgen therapy and surgery gives poorer results than either alone. He believes that radiation following operation and the employment of bone grafts may prevent creeping substitution in the grafts.

Hatcher, discussing Meyerding's presentation, says that it is possible that some benign giant cell tumors which have been reported to undergo malignant changes are examples of sarcoma induced by roentgen therapeutic ir-



a b c

Fig. 5. Case 3. H. B., 7 years of age. Localized osteitis fibrosa cystica. a, Before surgery, November 11, 1931; b, after 2,400 milligram hours radium, June 3, 1932; c, approximately 2 months after surgery, January 1933.

ritation, but emphasizes that this is true in cases treated in which the indications and dosage were not so well known and controlled as they are now.

Mandl does not favor preoperative irradiation.

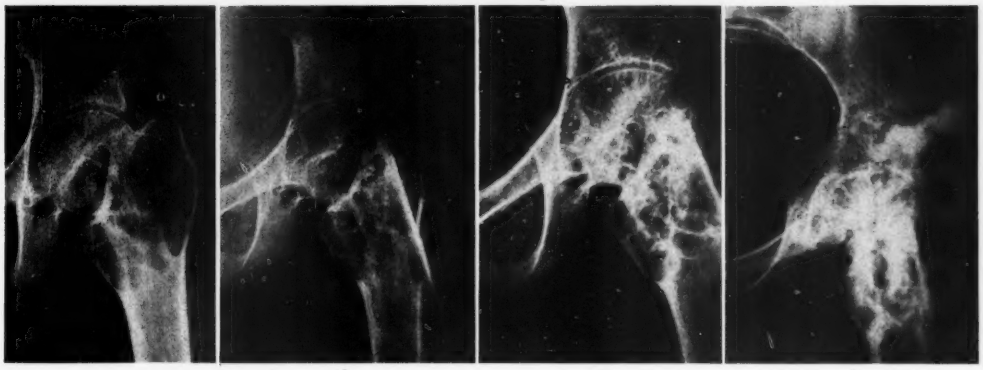
Cantril and Buschke state that roentgen therapy of giant cell tumors is a highly satisfactory procedure. They state that curettage is unsatisfactory because of the frequent recurrences (30 per cent). It increases the danger of infection and may make roentgen therapy more risky and difficult. They prescribe x-ray therapy in minimal dosage sufficient to destroy the tumor but not to interfere with regeneration of bone.

Haggart and Hare believe it erroneous to warn against combined radiation therapy and surgery in the management of giant cell tumor.

Woodard and Coley (42) after treatment of 11 giant cell tumors with irradiation have come to the conclusion that they should not be treated by irradiation.

Cahan and his associates feel that irradiation therapy is far less satisfactory than surgical treatment. Irradiation therapy carries the risk of inadequate treatment of a malignant tumor in the mistaken belief that it is benign, that many of these benign lesions are radioresistant or only slightly radioresponsive, that the growth centers of children may be seriously disturbed, and that sarcoma may develop at the site of previous irradiation.

They describe 11 cases in which bone sarcoma developed at a period long after irradiation of benign tumors. In our rather small series of proved benign giant cell tumors, 2 patients (H. D. and P. O'L.) developed post-irradiation sarcoma. The question arises whether these 2 patients may not have developed sarcoma if they had not had irradiation. The biopsy sections following the original surgery in these cases had been carefully checked by several pathologists. The entire tumor had been resected. It is presumed therefore that there had been no error in the original diagnosis, and that the resulting sarcomas had been caused by the irradiation.



a b c d

Fig. 6. Case 4. P. O'L., 15 years of age. Xanthomatous bone cyst left femur. a, March 5, 1936, on admission; b, July 7, 1936, after curettage and massive grafts and bone chips; c, April 1, 1937, healing; film made during x-ray therapy; d, April 4, 1940, 4 years postoperative, showing malignant degeneration of ilium and upper end of femur.

With these divergent expert opinions, how should the local clinician or radiologist decide upon the course to pursue in a given case? The majority of these patients are originally seen by men in general practice and the diagnosis is made with the assistance of the local roentgenologist. Too few of these patients are seen early by the expert roentgenologist, general surgeon, or orthopedic surgeon. A more definite conclusion regarding the method of treatment offering the best end result with a minimum of functional loss and minimal disability may only be determined by more extensive and better illustrated literature on this subject. Good roentgenographic reproductions showing the extent of involvement at various stages of the treatment and the end results, good, bad, or indifferent should be published.

Geschickter (14), in evaluating the treatment of giant cell tumor by surgery or irradiation, chooses a middle ground. He states that surgery can be used following irradiation if the latter is properly given, while irradiation following unsuccessful surgery is usually useless. H. Platt favors surgery in the treatment of benign giant cell tumors. Geschickter and Copeland (15) state that "excluding isolated giant cell tumors of the skull and vertebrae, curettage performed in carefully selected cases is unquestionably the treatment of choice." Bloodgood favored thorough curettage followed by cauterization with pure phenol, later neutralized by 95 per cent alcohol. Some surgeons use a 50 per cent zinc chloride solution. The electric cautery or soldering iron was often substituted for the chemical cauterization.

Herendeen (20, 21) favors primary roentgen therapy without operation. He gives "growth

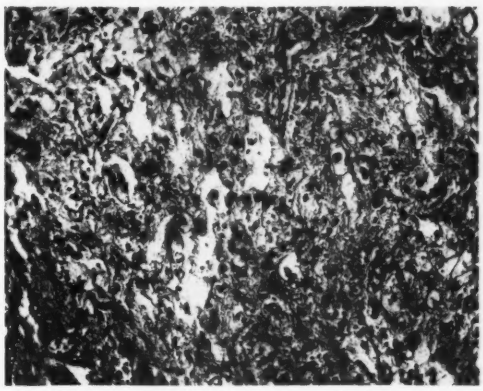


Fig. 7. Same patient as in Figure 6. Photomicrograph (×145) original biopsy. Tissue from the wall of the cyst reveals a very cellular fibrillar connective tissue infiltrated with small round cells. In places there are nests of large foamy cells with a small eccentric nucleus and vacuolated cytoplasm. Sudan 3 stain reveals the cytoplasm contains lipoid material. The contents of the cyst shows a similar structure with single foreign body giant cells. Single foci of new bone formation imbedded in the cellular tissue. The histological picture suggestive of xanthomatous bone cyst.

a b c

d e

Fig. 8. Case 5. J. S., 28 years of age. Benign giant cell tumor. a, b, and c, Anteroposterior, lateral, and oblique views showing lytic lesion of medial condyle; d and e, roentgenograms 5 months postoperative showing reconstruction.

restraint" dosages, which are followed by apparent tumor growth and later regression. Pain and tenderness diminish as the reaction subsides, ossification takes place, and function returns. Results are not evident for months.

Pierce (35) agrees with Herendeen and Pfahler. He favors frequent relatively mild doses of roentgen therapy with the purpose of growth restraint. It is his opinion that surgical intervention should not follow roentgen therapy short of 6 or 8 weeks. In his series of cases there was a less favorable response following surgical intervention. Pierce favors immediate roentgen therapy, if surgical intervention has already been accomplished, especially if there has been no cauterization at the time of operation.

While Pierce speaks of the "specificity of irradiation in inducing ossification of giant cell tumor and in the repair of malacic fracture in osteitis fibrosa cystica localisata," we have observed excellent spontaneous repair in the latter following fracture without irradiation or any other treatment except immobilization.

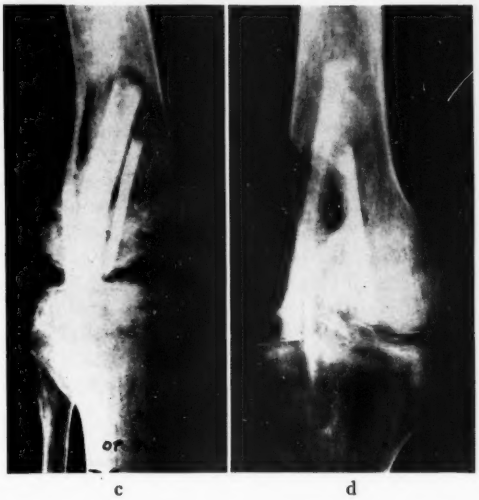
Pierce (33, 34, 36) reported 2 cases of malignant degeneration of giant cell tumor or of concurrent origin of malignant neoplasm.

W. B. Coley was opposed to irradiation following curettage, stating that either surgery or irradiation but not both should be used. It was his opinion that a higher percentage of malignant growths followed irradiation of benign lesions after surgery. Coley believed that 16 per cent of benign giant cell tumors became malignant. He favored surgery, cauterization, and complete closure of the wound.

Simmons, in a review of the cases in the registry of the American College of Surgeons, reports 3 cases or 3.7 per cent of benign giant cell tumors changed to osteogenic sarcoma, but there is no conclusive evidence that the original diagnoses may not have been erroneous. It is frequently possible for a poorly located specimen to be given to the pathologist for the original diagnostic examination. The biopsy specimen may be taken from a portion of the mass which is not typical of the tumor proper. *The pathologist can only report on the specimen presented to him by the surgeon.*

a

b



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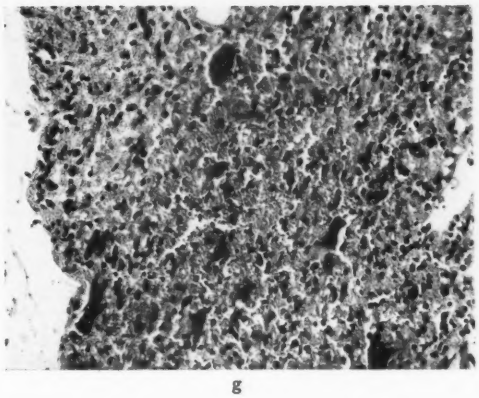
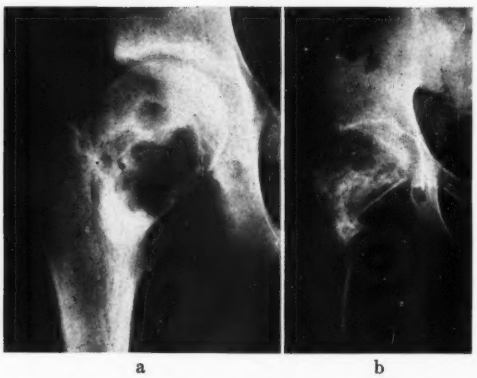


g

Fig. 9. Case 6. D. G., 39 years of age. Benign giant cell tumor. a, Original roentgenogram; b, after 2 months of irradiation; c and d, after resection and reconstruction; e and f, approximately 2 years postoperative; g, at right, photomicrograph (×180), giant cell tumor. Note the presence of multinucleated giant cells in a rather loose stroma. Hematoxylin eosin preparation.



a b

Fig. 10. Case 7. E. G., 15 years of age. Localized osteitis fibrosa cystica neck of the left femur. a, Before surgery; b, reconstruction with iliac grafts. Roentgenograms 2 months postoperative.

Biopsy specimens should, therefore, be taken from the depth and also from various areas of the tumor mass and preferably en bloc.

Stone and Ewing reported a case of malignancy of bone occurring at least coincidentally with a giant cell tumor.

Mercer reports recurrence following curettage. He evidently feels that some of the giant cell tumors undergo malignant degeneration, and that some are infected and in other cases there is failure of healing of the large cavity. He states that "deep x-ray therapy gives reasonable hope of permanent cure although in 3 or 4 weeks after treatment, the appearance is that of a rapidly growing malignant tumor. This acute phase quickly subsides and fibrosis with rapid regression of the tumor results."

Jones and Lovett describe the giant cell tumor as a collection of spindle cells with numerous multinuclear giant cells. The growth has no tendency to metastasize and can be removed locally.

While most authors have discarded the term "sarcoma" for that of benign giant cell tumor, it is regrettable that Whitman states that "in comparison with most sarcomata, giant cell sarcoma is a tumor which is clinically benign." Baetjer and Waters have a page on "giant cell sarcoma" and then state that it has a "malignant name but is entirely benign in character," and Albee under the title, "The Treatment of Primary Malignant Changes of Bone by Radical Resection and Bone Graft Replacement," includes in his report 2 and perhaps 3 cases of benign giant cell tumor. Such repetition of errors of nomenclature confuses the students and clinicians and should be eliminated from the literature.

The writers present some cases of benign lytic bone lesions, treated by curettage, aspiration, primary excision or resection, followed by immediate reconstructive surgery. The technique described has the following advantages: (1) more definite and time saving end results; (2) immediate cessation of the destructive process, diminishing the extent of necessary reconstruction in direct proportion to the time elapsing since onset.

At operation, under tourniquet, an incision is made directly into the tumor which in benign giant cell tumor consists of a current jelly, fleshy mass containing some serosanguineous fluid. Frozen section confirms the diagnosis in the operating room and the writers proceed with the technique of resection. Depending upon the size, location, and nature of the lesion it may be eradicated by a thorough intrinsic curettage or by an extrinsic total resection.

In the intrinsic method a long window is cut over the tumor so that all sides and ends are in full view. The mass is resected grossly and then a curette is employed, at the same time constantly using a large caliber rubber suction tube attached to a strong suction apparatus (Fig. 1). Substitute hose is at hand to be changed as frequently as is necessary during the operation. Each loculus is cleansed of tumor tissue with the curet and the suction apparatus. When the entire inside of the cavity can be seen thoroughly cleansed of tumor tissue, a ball electrode endotherm is used to cauterize the entire wall. It is then filled with saline solution, the large suction tube is again inserted and the walls are again curetted, and the contents thoroughly aspirated. For the bone grafts, cancellous bone is obtained from the wing of the ileum. Mowlen and Abbott and associates have shown that cancellous bone is able to withstand infection to an unusual degree, because of its loose structure it acquires an adequate blood

a

b

c

d

e

Fig. 11. Case 8. S. G., aged 58 years. Fibrous dysplasia of bone. Hyperparathyroidism. a, Roentgenogram before surgery showing the lytic lesions of the ilium, ischium, and pubis; b, roentgenogram 2 weeks later showing negative urography and apparent progression of the lesion of the left ilium; c, roentgenogram showing a lesion in the lower end of the right humerus; d, roentgenogram showing healing of lytic lesions 3 months after parathyroidectomy; e, roentgenogram 7 months after removal of parathyroid adenoma showing complete reossification of the lesions of the pelvis.

supply sooner, retains its cellular activity with greater osteogenic power, and undergoes the changes rapidly necessary to suit it to its new environment.

These bone chips are used to pack the cavity. Where structural support is necessary long cortical bone grafts are obtained from the tibia and used in strut-like fashion in the longitudinal axis of the cavity. The soft tissues are sutured tightly by layers, with chromic catgut used throughout including the skin so that dressings are unnecessary. A well fitting plaster cast is applied. This remains on for approximately 3 months, during which time check-up roentgenograms are made at intervals of 4 to 6 weeks. When indicated, a brace is used after the removal of the cast.

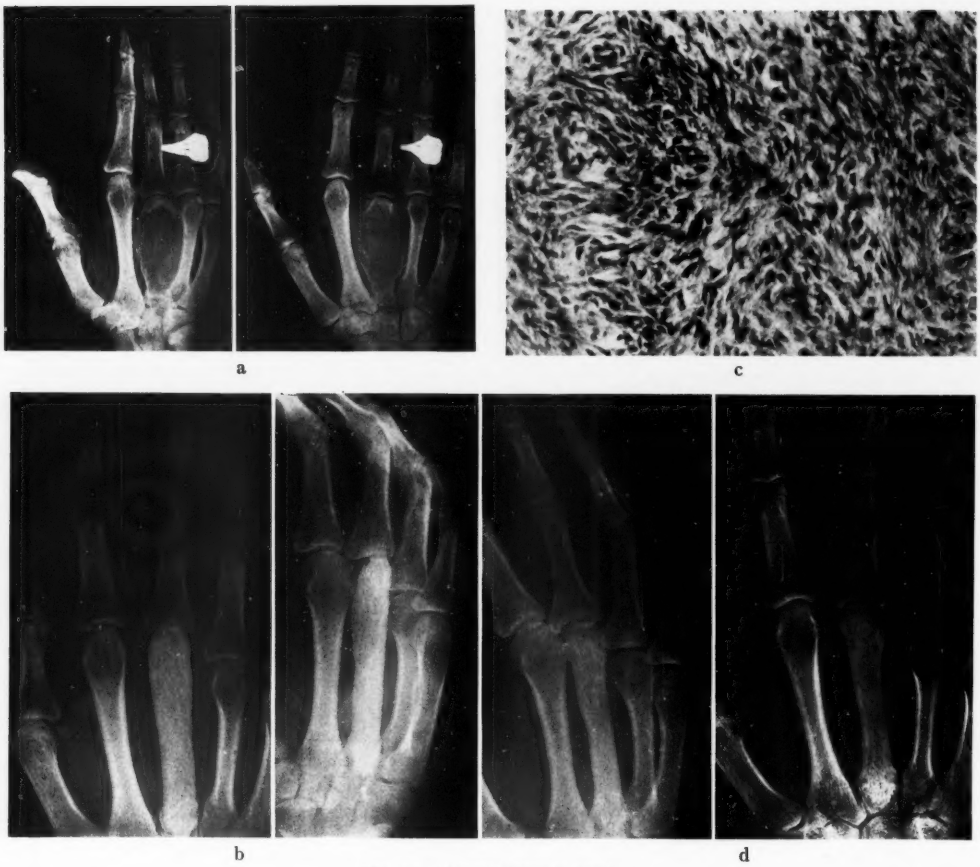


Fig. 12. (*Legend opposite page*).

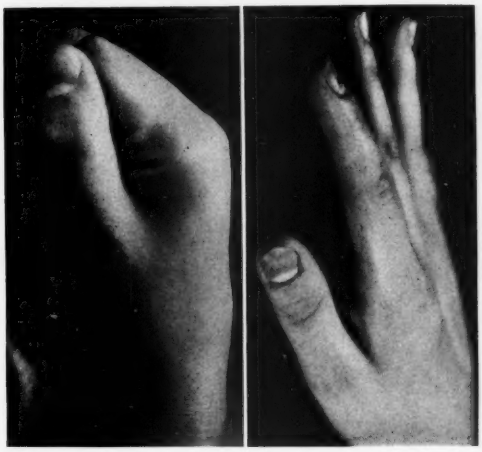
The extrinsic or total extraperiosteal resection is done in cases in which there is extreme thinning out or destruction of the cortex. Reconstruction is done by the use of thick autogenous bone grafts for structural support with numerous cancellous bone chips for its osteogenic power. Wherever applicable anatomical reconstruction should be attempted (Levinthal and Kirshbaum).

For several years, the writers have used a technique of small pedicled tooth-like grafts across the tibial channel of the donor site to hasten regeneration of bone following removal of massive grafts (Fig. 2). This method also prevents depression of the scar.

CASE REPORTS

CASE 1. A. K., aged 10½ years, Michael Reese Hospital. In 1933, the patient fell from a tree and fractured his left shoulder. In January 1936, the same shoulder was injured when struck by a truck. In April, 1936, the same shoulder was again injured by falling. Examination at this time revealed a fusiform tender expansion of the proximal end of the right humerus. Roentgenogram showed a multilocular cystic area expanding the upper one-third of metaphysis (Fig. 3, a). There was no evidence of a pathologic condition in any of the other long bones.

Operation was performed on May 19, 1936. Curettage and aspiration were done followed by the use of tibial grafts to fill the defect. The pathologist's diagnosis concurred with the clinical diagnosis of osteitis fibrosa cystica. Patient made uneventful recovery with a complete return of function (Fig. 3, b).



e

f

Fig. 12. Case 9. B. S., 16 years of age. Fibroma of the middle metacarpal bone. a, Roentgenogram before operation, showing expanding lytic tumor of the middle metacarpal bone. Complete destruction of the shaft including cortex, some trabeculation. There is a thin remnant of bone of fairly normal density in the subchondral region of the head of the metacarpal, and about 1 centimeter of normal appearing bone at the proximal end. Note the shortening of the metacarpal; b, roentgenogram showing reconstruction of metacarpal by tibial graft. Note restored length of the finger; c, photomicrograph of the tumor mass. Note the dense fibrillar appearance of the lesion and in one area a spicule of bone; d, roentgenographic appearance 27 months after operation showing transformation of graft into a true metacarpal bone; e, photographs showing extension and flexion; f, photographs 27 months after operation showing restored length of right middle finger, full extension, and very moderate limitation of flexion.

Case 2. N. O'B., aged 4 years, Michael Reese Hospital. There was a history of right limp and pain in the right hip region of 3 months' duration. The physical examination revealed tenderness about the right great trochanteric region, swelling, and limp. There was no local heat or redness. Roentgenograms revealed a multilocular cystic lesion of the proximal metaphysis of the right femur extending to the epiphyseal plate (Fig. 4, a).

At operation on August 15, 1936, a window was opened into this cavity. This was curetted, aspirated, cauterized with 50 per cent zinc chloride solution, washed and again aspirated. The cavity was then filled with cancellous bone chips taken from the ilium. The pathologist's report was osteitis fibrosa cystica with giant cells (Fig. 4, b).

Recovery was uneventful, and the follow-up roentgenograms show gradual reossification of the involved area and reconstruction of the normal architecture of the upper end of the femur (Fig. 4, c). The patient has had no residual symptoms.

Case 3. H. B., aged 7 years, Michael Reese Hospital. There was a history of pain and swelling of the right forearm following an injury of about a week's duration. Roentgenograms showed an expanding cyst of the left ulna. The patient had 2,400 milligram hours of radium on November 17 and 18, 1931. November 8, 1932, because of expansion of the cyst, operation was advised. Through a small incision, the cyst wall was opened, curetted, and aspirated, and the lateral wall gently compressed with the flat surface of a small periosteal elevator. On January, 1933, check-up of roentgenograms show regeneration of bone within the former cystic area. Eventually there was recovery of form and function and the patient was symptom free.

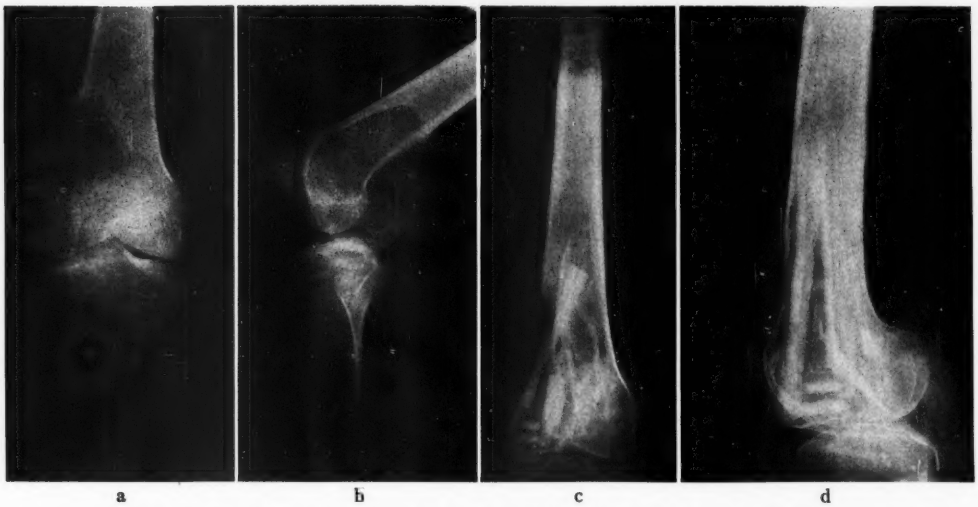
Case 4. P. O'L., aged 15 years, Cook County Hospital. Patient gave history of developing pain and limp in left hip about December 1934. In March of 1935 while walking her leg suddenly gave way. She was admitted to the hospital on March 12, 1936. Roentgenogram taken at this time (Fig. 6, a) showed a multilocular area in the upper end of the left femur and a pathological fracture of the neck of the femur.

Surgery was performed on March 23, 1936 at which time the large yellow tumor mass was curetted, aspirated, and cauterized. Bone grafts obtained from the tibia and the ilium were used to fill the bone defect. The microscopic diagnosis of this tumor was xanthomatous bone cyst (Fig. 7).

The patient's postoperative course was smooth. She received x-ray therapy as a part of her follow up treatment. Roentgenograms April 1, 1937 show regeneration of bone in the pre-existing cavity with union of the fractured neck of the femur (Fig. 6, c).

Four years later patient complained of pain, loss of weight, and swelling localized to left hip region. Roentgenograms showed sclerosing osteogenic sarcoma verified by biopsy. The patient died of pulmonary metastases about 1 year later.

Case 5. J. S., aged 28 years, Michael Reese Hospital. Patient gave a history of pain first developing in the region of the left knee in November, 1935. Consulted us on February 15, 1936. Examination revealed moderate tenderness over the medial condyle of the left femur and an eggshell feeling or crackling on deep pressure over that area. Roentgenograms (Fig. 8 a, b, c) show a lytic lesion with slight trabecu-



a b c d

Fig. 13. Case 10. Y. B., aged 22 years. Benign giant cell tumor of the femur. a and b, Before operation; c and d, after resection and reconstruction.

lation involving the medial condyle of the left femur. The Wassermann and Kahn tests were negative.

On February 29, 1936, surgery was performed. The tumor was excised grossly and frozen sections showed benign giant cell tumor, highly cellular. Thorough curettage, irrigation suction, and cauterization with a ball electrode endotherm were used. The defect was filled with numerous cancellous grafts as well as cortical strut grafts obtained from the tibia. Cast was applied. The cast was removed 3 months later. Roentgenograms taken July 27, 1936 show reconstruction (Fig. 8 d, e).

Case 6. D. G., aged 39 years, Michael Reese Hospital. The patient gave a history of pain in the left knee since 1931. From then until 1934 he had been treated for "rheumatism." In April 1934 he slipped while getting out of the bath tub and forcibly bent his left knee causing a loud crackling and tearing of the joint. He had a great deal of pain and disability until he was seen at a clinic on May 1934, at which place he was told he had a tumor requiring irradiation. He was also informed that he had a 3 plus Wassermann and diabetes. He was given deep x-ray therapy until July 11, 1934, at which time further roentgenograms were made. The patient was then told he had a malignant tumor requiring amputation. He was admitted to the Michael Reese Hospital on July 20, 1934. The Wassermann and Kahn tests were negative and there was no glycosuria, nor hyperglycemia.

On July 21, 1934, the patient was operated upon. The mass was completely excised including the medial articular surface of the condyle since the tumor involved the entire subchondral plate. The soft structures and remaining bone surfaces were carefully curetted and irrigated, the large tube suction apparatus being used frequently. A ball electrode endotherm was used for cauterizing. Two cavities were then made into the head of the medial articular surface of the tibia and numerous strut grafts were taken from the tibial shaft and placed across from the shaft of the femur into the tibial head (Fig. 9). A spica cast was applied for 3 months followed by the use of a walking caliper brace. Brace was discarded in November 1935, at which time patient had an excellent fusion.

Case 7. E. G., aged 15 years, Michael Reese Hospital. The patient was observed in October 1941, complaining of pain, limited motion, and limp. The symptoms were all referred to the region of the left hip. Operation consisted of an anterior approach to the neck of the left femur. Curettage, aspiration, and cauterization were followed by the insertion of grafts obtained from the wing of the ilium. Roentgenograms made January 10, 1942 (Fig. 10 b) show the reconstruction. Six months postoperatively the patient was symptom free.

Case 8. S. G., aged 58 years, St. John's Hospital, Santa Monica. The history is that of pain in the left groin and anterior aspect of the left thigh of 8 months' duration. On October 2, 1947, the patient presented himself in the out patient department of St. John's Hospital walking with the aid of crutches. His condition had been studied at another clinic and diagnosed as metastatic carcinoma of the bones, because of numerous lytic lesions involving the wing of the left ilium extending into the acetabular cavity, the right elbow, ischium and pubes, and the region of the left lessor trochanter. Additional lesions were noted in the left femur, both ilia, and the skull.

A complete study revealed no primary lesion. The patient had lost no weight. The routine blood count was normal. Blood chemistries showed calcium of 13.5 milligrams per cent, phosphorous 0.9 milligrams per cent, and alkaline phosphatase of 1.7 King-Armstrong units. There was hypercalcinuria. The sedimentation rate was 40 millimeters in 1 hour. Recheck blood calcium was 15 milligrams per cent. On November 15, 1947, a biopsy was taken from the large lesion in the supra-acetabular region of the left hip (Fig. 11 a). The pathologist, Dr. Hummer, reported fibrous dysplasia, confirming the clinical diagnosis.

On December 9, 1947, the neck was explored. A benign calcified adenoma of one of the left parathyroids was removed from within the capsule of the thyroid gland. The blood chemistries immediately returned to normal values. Subsequent roentgenograms showed gradual recalcification of the lytic bone lesions (Fig. 11, d, e).

On observation in the clinic in September 1948, the patient walked without crutches and with a slight limp. He had no pain and had returned to his previous occupation. The blood chemistries remained normal.

CASE 9. B. S., aged 16 years, Cook County Hospital. This patient was first seen in the out patient clinic on February 11, 1936. The complaint was a progressive swelling of the dorsum and palm of the right hand. This was first noticed about a year prior to her admission to the Cook County Hospital. The roentgenograms showed a lytic expanding tumor of the middle metacarpal bone with absence of the cortex along parts of the shaft. The base was uninvolved for about 1 centimeter (Fig. 12, a).

Operation was performed on February 12, 1936. The entire mass was carefully resected, including the metacarpal head. The base was not resected, but was excavated to receive a metacarpal shaped, measured graft from the tibia. The pathologist reported fibroma of bone. The patient made an uneventful recovery with almost complete return of form and function. The smooth graft eventually developed the contours of a metacarpal bone, including a narrow cavity (Fig. 12, d).

CASE 10. Y. B., aged 22 years, Michael Reese Hospital. There was a history of pain and limp in the left knee beginning several months prior to observation at Mandel Clinic. Roentgenograms made November 29, 1941 showed an expanding lesion of the medial condyle of the left femur (Fig. 13, a and b). The patient was operated upon several weeks later at which time frozen section biopsy by Dr. Otto Saphier confirmed the clinical diagnosis of benign giant cell tumor. Through an adequate window, the contents of the tumor mass were completely resected, curetted, aspirated, irrigated, fulgurated with the ball electrode endotherm, and packed with long tibial struts and cancellous bone grafts. A long plaster of paris spica was applied. Subsequent roentgenograms showed reconstruction of the medial condyle and proliferation of the grafts. After the cast was removed 3 months postoperatively, a walking caliper brace was applied for 9 months. With physical therapy, the patient obtained a 90 degree range of painless motion with excellent stability.

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TRANSVERSE INCISION FOR PYLOROMYOTOMY

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THE surgical management of infants with hypertrophic pyloric stenosis is now well standardized and highly successful. Its low mortality has been brought about by two factors. One is the introduction of the operation of dividing the muscular fibers of the pylorus longitudinally as is practiced universally at present, this operation having been developed by Frédet (6), Weber, and Rammstedt. Almost immediately following the introduction of this operative procedure the mortality figures improved. This less formidable operation brought about the results which had formerly been attained only by such a procedure as gastroenterostomy, a serious operation in the first few weeks of life.

The other factor is one that developed more gradually; that is the improvement in preoperative and postoperative care. No longer are these patients operated upon as emergencies. Dehydration, acidosis, anemia, and avitaminosis are corrected prior to surgery. Postoperatively the prompt resumption of feeding, in most cases within 24 hours after operation, and careful attention to caloric needs and fluid balance have further improved the results. In fact, series of cases numbering 310 (Donovan, 5), 225 (Ladd, 12), 172 (Schaefer and Erbes), and 167 (Strauss) have been operated upon without a death. The mortality in complete series reported by these authors is 0.24 per cent (Donovan), 0.9 per cent (Ladd), 3.8 per cent (Schaefer and Erbes), and 2 per cent (Strauss). The average mortality figures in the reports collected and summarized by Szilagyi and McGraw, however, was 7.9 per cent. These reports covered the years 1923 to 1941 but, as in most studies, there has been a steady decrease in the mortality in more recent years due to increasing experience with the operation and improvement in the preoperative and postoperative management. Currently, immediate satisfactory results may be anticipated in 97 to 98 per cent of the operative cases with a rate for reoperation of 2 to 3 per cent and an average mortality figure of between 1 and 2 per cent (22).

Nevertheless, wound disruption continues to be a serious, though infrequent, complication and has accounted for fatalities in some series. Ladd (10) ascribed 3 deaths in his series to evisceration. Two patients in another series by the same author and his associates (12) suffered dehiscence of the wound but resuturing was successful. In the series of 84 cases from Cook County Children's Hospital studied by Oberhelman, disruption of the wound occurred twice with fatal outcome in both instances. Donovan (3) reported 3 instances in 119 cases. Schaefer and Erbes reported 4 dehiscences of which 1 was fatal.

It has long been understood that very careful closure of the abdominal wall in these cases is necessary. This has been emphasized by Ladd and Gross (11) who point out that usually the abdominal wall is only 1/8 to 3/16 inch thick (3 to 5 mm.). The well established type of incision is a vertical one through the right rectus muscle beginning at the costal margin and made deliberately over the liver so that the liver will form a barricade against the wedge effect of the omentum and other smaller structures when the incision is closed. The rectus muscle is either split or retracted laterally before the posterior rectus sheath and the peritoneum are opened vertically. In either case, a certain number of wound disruptions have occurred with this incision.

That this vertical type of incision is not uniformly satisfactory is indicated by the variety of other incisions recommended. Thus, Robertson advocated a gridiron incision made lateral to the rectus muscle and below the costal margin. This incision, while separating structures of the abdominal wall according to their lines of cleavage and direction of fibers, has all of the advantages of the McBurney incision in that respect. However, it is located at a point where delivery of the pyloric tumor

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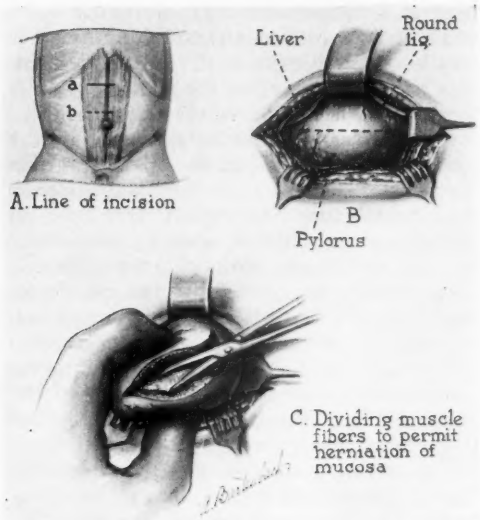

Fig. 1. Incision is made at level of previously palpated pyloric tumor. Note how pylorus fills the incision preventing extrusion of other structures.

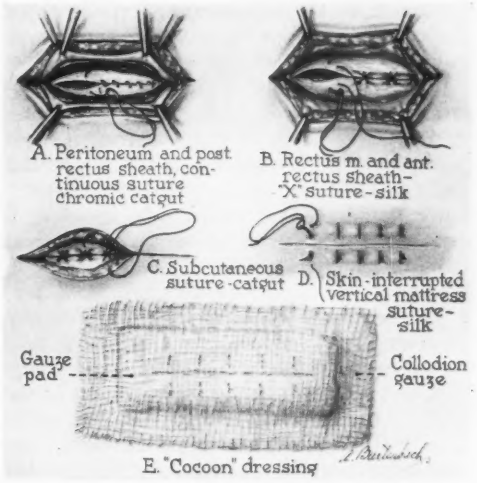
A. Peritoneum and post. rectus sheath, continuous suture chromic catgut
B. Rectus m. and ant. rectus sheath-"X" suture-silk
C. Subcutaneous suture-catgut
D. Skin-interrupted vertical mattress suture-silk
Gauze pad
Collodion gauze
E. "Cocoon" dressing

Fig. 3. Closure of the transverse incision.

through the incision is not always easy, and many times considerable trauma to the stomach, the omentum, and perhaps to the transverse colon may result from attempts to deliver the pyloric tumor.

Much has been written concerning the advantages of transverse incisions (7, 8, 16, 18), and it is generally conceded that with them (a) the tension in the area of the incision is principally parallel to the incision itself, (b) there is less wound disruption, and (c) patients are much more comfortable. The first two of these advantages have apparently prompted the use of many modifications of this type of incision in the surgical treatment of hypertrophic pyloric stenosis. Thus Davis described an incision which is transverse through all the layers of the abdominal wall except the rectus muscle which is split vertically. Meredith described an incision vertical through all layers except the posterior rectus sheath and peritoneum which were divided transversely. The rectus muscle was split. Brunkow advocated a high right rectus transverse incision. Singleton, in discussing Robertson's paper, described the incision he favored. It is essentially the same as Meredith's, and he emphasized that with the transverse incision there was no room for evisceration of omentum and bowel. Horgan pointed out the advantages of a high transverse incision through all layers of the

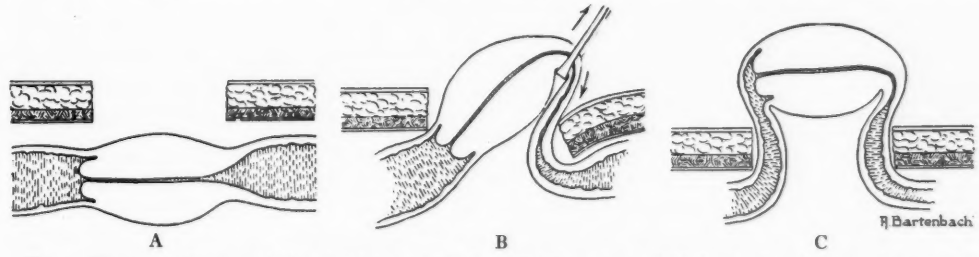

Fig. 2. Diagrammatic presentation showing method of delivery of pyloric tumor through small incision. Downward pressure on abdominal wall makes excessive traction on pyloric attachments unnecessary.

abdominal wall except the rectus muscle which is dissected from the anterior rectus sheath and retracted medially.

It is true that most of the infants with hypertrophic pyloric stenosis will do well regardless of the type of incision, their general condition being favorable to adequate wound healing. However, in the poor risk patients, many of which are operated upon under local anesthesia, the type of incision which is least liable to undergo dehiscence is desirable.

The transverse incision recommended here is approximately 4 centimeters long, divides all layers including the right rectus muscle transversely, and may be located anywhere from just below the costal margin down to the level of the umbilicus (Fig. 1A) depending upon the point at which the pyloric tumor has been palpated prior to operation. The incision need not be longer since in typical cases properly investigated, there should be very little if any doubt about the diagnosis, therefore, no need for any but regional exploration. In rare instances in which the diagnosis is uncertain, it may be verified at operation by the introduction of one finger into the abdomen.

All intra-abdominal manipulations are done with instruments, principally Babcock forceps and tissue forceps without teeth. Since the incision is made at a level which corresponds to the location of the pyloric tumor, the first structures encountered may be the edge of the liver or the anterior wall of the stomach. With the body and the fundus of the stomach collapsed, due to the presence of an inlying catheter in the stomach, it is possible to pass the wall of the stomach to the left and by doing so the pylorus can be brought to a point just underlying the incision.

It is not necessary to bring any structure except the pylorus outside the abdomen (Figs. 1B, 1C). Since the average dimensions of the pyloric tumor are approximately 2 centimeters in length and about 1.5 to 2 centimeters in diameter, with a wall .5 to .8 centimeter thick (22) there should be no difficulty in delivering the pyloric tumor through the transverse incision. The gastric end of the tumor is brought up first, as shown in Figure 2B. In this way, a pyloric tumor even longer than the incision may be brought outside the abdominal wall (Fig. 2C). Since the incision is usually made at some distance from the costal margin, it is possible to press down on the anterior abdominal wall and thus allow the tumor to be delivered outside the abdominal wall without excessive traction on the attachments of the pyloric area. As some of the bleeding in this divulsion is thought to be due to traction on the attachments of the pyloric area with resulting interference with venous return, there may be less difficulty with hemostasis. At this point, it may be noticed that the pyloric tumor, lying transversely and being brought up through the transverse incision, closes off practically all of the incision (Fig. 1B) and leaves no room above or below the pylorus for the herniation of omentum or small bowel such as frequently happens in the vertical incisions.

The divulsion or division of the circular fibers of the pylorus is then done in the usual manner with precautions against perforating the duodenal mucosa but with care that all fibers are divided sufficiently to a point where the normal thickness of the seromuscular layers of duodenum and the stomach is reached. A binocular loupe or other visual aid may be used, not so much to insure the division of every single muscle fiber, but rather to guard against perforation of the duodenal mucosa. Robertson believes that squeezing the duodenal end of the tumor between the left index finger and left thumb causes a change in the relationship of the muscle mass to the duodenal mucosa so that splitting the muscle mass can be accomplished with less danger of perforating the duodenal mucosa.

The closure of the wound is easy (Fig. 3). The edges of the posterior rectus sheath and peritoneum can be approximated easily even if the patient is straining. This is certainly not the case when these layers have been divided vertically. The rectus muscle is sufficiently adherent to the anterior rectus sheath to prevent marked retraction. However, approximation of the rectus muscle is indicated because it obliterates any dead space which might otherwise result and in which serum might collect. This can be accomplished by means of X sutures of fine chromic catgut or by catching the muscle edges in the fascial sutures. The closure of the rectus sheath is ac-

complished by means of interrupted X sutures of fine silk and the subcutaneous tissue and the skin are approximated with fine catgut and silk respectively.

It is agreed that the cosmetic result is of minor importance. Even the vertical incision with broadening of the scar becomes proportionately less conspicuous as the child grows. However, with the transverse incision, after 2 or 3 months, it may be difficult to see the incision except upon very close inspection in good light. The incision as described herein has been used in a series of 34 personal cases with no instance of wound disruption.

SUMMARY

Various abdominal incisions used in the surgical treatment of congenital hypertrophic pyloric stenosis are presented. A transverse incision through all the layers of the abdominal wall including the right rectus muscle and at the level of the previously palpated pyloric tumor is described and discussed in detail. It has been entirely satisfactory in a series of 34 of the author's cases.

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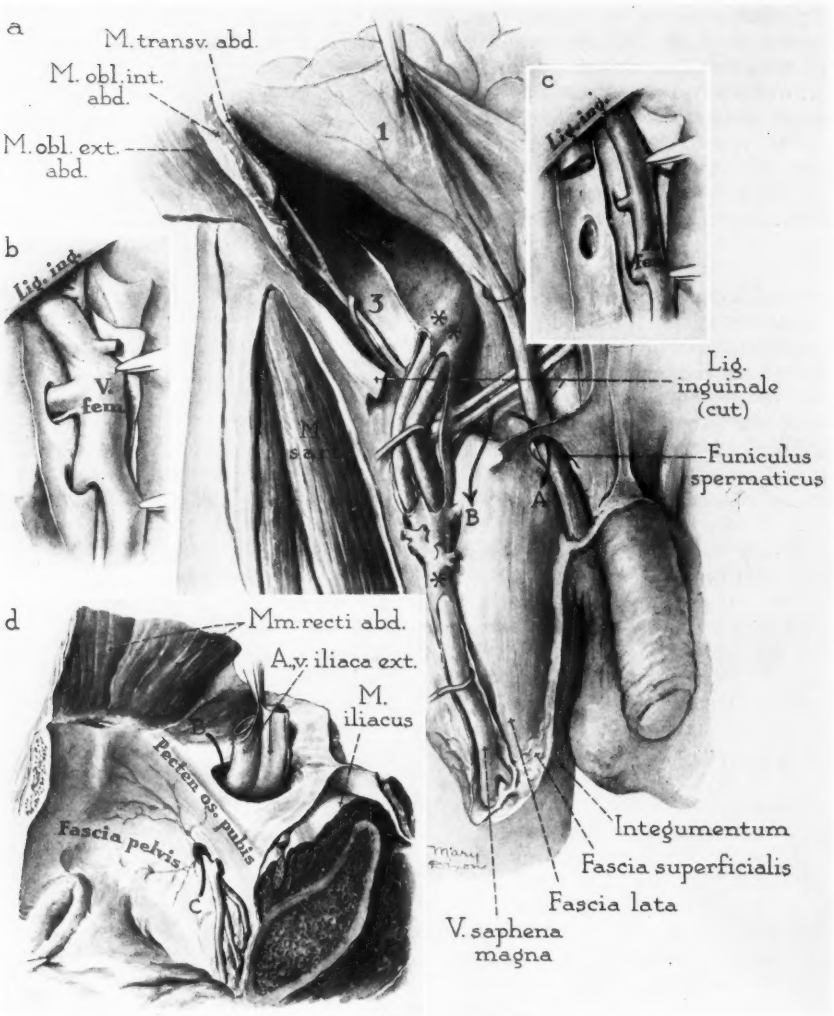

Fig. 3 (*Legend on opposite page*).

The Anatomy of the Hernial Regions; II. Femoral Hernia.—
Barry J. Anson, Arthur F. Reimann, and La Vern L. Swigart

THE ANATOMY OF HERNIAL REGIONS

II. Femoral Hernia

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CONTINUING a report upon their study of the anatomy of the important hernial regions, the authors will herein record their dissection-experience with the strata which, passing from abdomen to pelvis, converge upon the large vessels in the proximal part of the thigh and form sheaths for the femoral artery and vein.

MATERIAL AND METHODS

For the present account the authors depend chiefly upon three particularly favorable specimens, each of them a well developed adult. Two male cadavers were employed to illustrate the normal anatomical relationships of structures of the inguinal wall, pelvic cavity, and proximal thigh (Figs. 2a and 2b, 3a to 3d); a female specimen was utilized for drawings of the same structures, as affected by a femoral hernia (Figs. 4a and 4b, 5a and 5b, 6a to 6c). In order to record pertinent morphology of the region where a femoral hernia reaches a subcutaneous, palpable position, variations in the fossa ovalis and its vascular contents are pictured (Figs. 1a to 1f), and statistical data are presented.

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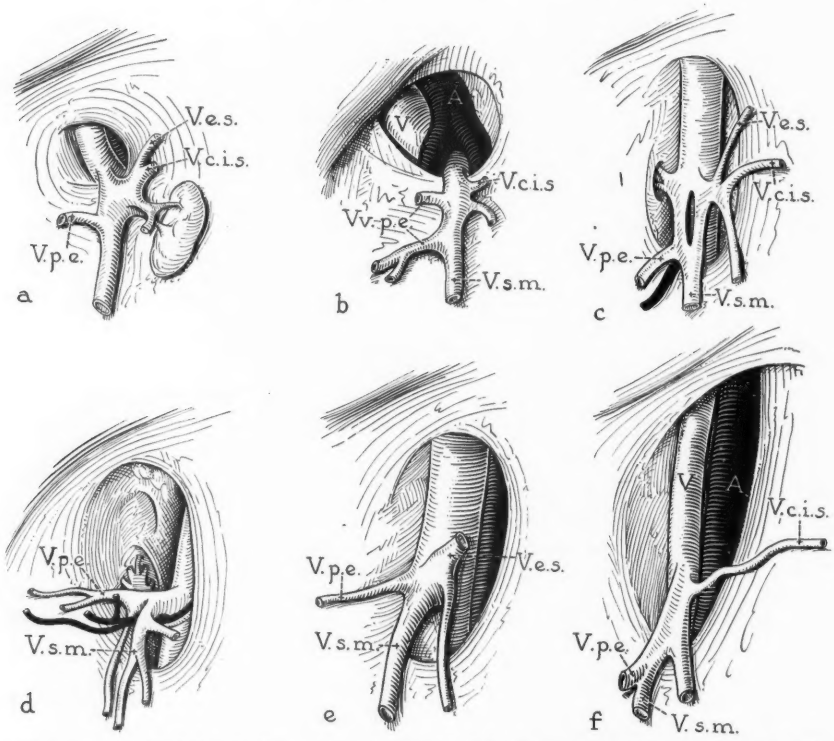
OBSERVATIONS AND DISCUSSION

In contrast to the movable, and often pedunculated, indirect inguinal hernia, the mass of a femoral hernia appears to be little more than a swelling in the upper and inner angle of the femoral (Scarpa's) triangle. Here it is usually situated below and to the side of the pubic tubercle and below the inguinal ligament; however, sometimes the upper part of the mass may extend above the ligament.

In descending from an abdominal to a femoral position, under the ligamentous edge of the external oblique and upon the superior pubic ramus, a herniating mass (intestinal or omental) pushes ahead of it the deeper layers of inguinal position to a point where, in or beyond the fossa ovalis, the hernia acquires additional coverings from the overlying layers of the thigh. Having reached subfascial level in the thigh, the hernia elevates the overlying skin.

Figs. 3a to 3d. Structures related to the regions of inguinal, femoral and obturator herniae. Specimen II. Fig. 3a. The abdominal layers have been incised along the inguinal ligament; the peritoneum (at *1*), with the coils of small intestine, has been lifted to show the preperitoneal connective tissue (at *2*). The sites of inguinal and femoral herniation are indicated by arrows *A* and *B*, respectively. The site of the orifice of the abdominal inguinal ring is marked by a circle. The fascia lata has been reflected to expose the sartorius muscle, as the latter forms the latter boundary of the femoral triangle. The preperitoneal (subserous) layer (indicated by **) is carried downward from the iliac vessels upon their femoral continuations (at *); from these larger vessels arise the deep circumflex iliac and the inferior epigastric branches (unlabeled), from lateral and medial sides, respectively. Fig. 3b. The femoral sheath of the opposite thigh has been opened to show the femoral vein; the vessel has been retracted in order to demonstrate the manner in which its tributaries are invested by tubular continuations of the sheath. Fig. 3c. The vein has been removed to demonstrate similar relations of the corresponding artery. Fig. 3d. Anterolateral portion of a pelvis, viewed from within; sagittal section to the left of the midline. Specimen III. The viscera and subserous tissue have been removed; the external iliac vessels have been cut and lifted in order to emphasize the tubular character of the vascular lacuna. Medial to the vein is the femoral ring (at arrow *B*). Vessels converge upon the internal orifice of the obturator canal (arrow *C*). The iliacus and psoas muscles and the femoral nerve occupy the muscular lacuna.

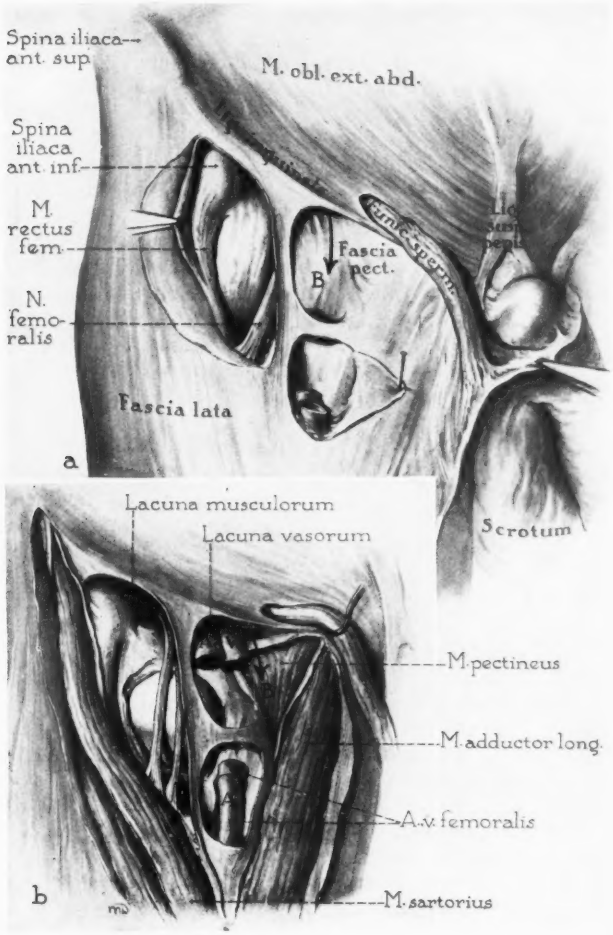
An indirect inguinal hernia would transverse the inguinal canal in indirect course, from the abdominal orifice (encircled by the ring), through the subcutaneous fault in the fibers of the external oblique aponeurosis (at arrow *A*, Fig. 3a, between the crura of the ring) to some point beyond the aponeurotic hiatus. Its immediate investment would be the peritoneum, which, as a vaginal process, would be progressively dilated as herniation progressed (see article I). A femoral hernia would, in a more direct course, pass beneath the inguinal ligament upon the pecten of the pubis and between the lacunar ligament medially and the femoral vein laterally (at arrows *B*, Fig. 3a and Fig. 3d). An obturator hernia would enter the internal orifice of the obturator canal (Fig. 3d, at arrow *C*). The further course of an obturator hernia is pictured in article III.



Figs. 1a to 1f. Variations in form, size, and contents of the fossa ovalis. Examples arranged in the order of increasing dimensions, from the smallest to the largest encountered in a series of 200 lower extremities. All are examples of the left thigh. In the specimens shown in Figures 1a and 1e, the femoral artery is but slightly exposed to the side of the femoral vein; in those depicted in Figures 1c and 1d the artery is wholly concealed beneath the falciform margin of the fossa; in those illustrated by Figures 1b and 1f it is fully exposed, in the former instance overlying the point of termination of the saphenous vein in the femoral. Abbreviations: *V. c. i. s.*, Vena circumflexa ilium superficialis; *V. e. s.*, Vena epigastrica superficialis; *V. p. e.*, Vena pudenda externa; *V. s. m.*, Vena saphena magna. The unlabeled vessel, ascending near the great saphenous vein, is the accessory saphenous vein.

Before considering these layers in detail, as evidenced in the selected case of femoral hernia (Figs. 4 to 6), it may be profitable to review their disposition in relation to such a hernial protrusion, that is, as elements which guide the hernia in its descent and as structures to which the hernia becomes secondarily related.

At the termination of its migration from the abdominal cavity into the thigh, the hernia attains subcutaneous position at the fossa ovalis (saphenous opening), where the degree of its prominence depends chiefly upon the dimensions of the fossa and upon the extent of its occupancy by blood vessels (Figs. 1a to 1f). In order to reach the thigh, the hernia is obliged to pass beneath the inguinal ligament, which, through its nearness to the resistant superior pubic ramus, constitutes a temporary hindrance to its descent (Figs. 2a, 2b, and 3a, at arrows *B*). The hernia emerges beneath the superior horn (cornu) of the fossa's falciform margin (compare Fig. 1e), resting upon the fascial covering of the pectineus muscle (Figs. 2a and 2b); in so doing, it has traversed the vascular lacuna of the subligamentous space, occupying the "space" medial to the femoral vein (Fig. 2b). Space exists,



Figs. 2a and 2b. Two stages in the dissection of spaces and contained structures in the inguinofemoral region. Specimen I. Fig. 2a. The superficial fascia has been removed, exposing in the inguinal and proximal femoral regions, respectively, the aponeurosis of the external oblique muscle and the fascial investment (fascia lata) of the muscles of the thigh. The external spermatic fascia has been removed in order to expose the spermatic cord and the crural boundaries of the subcutaneous inguinal ring. The femoral vessels have been excised from the fossa ovalis (saphenous opening). The course of a femoral hernia is indicated by the arrow *B*, which here emerges from the femoral ring. Distal to the fossa ovalis an artificial window has been cut in the fascia lata to demonstrate the further course of the femoral vessels (transected). A similar opening has been made in the fascia, lateral to the fossa ovalis, into the space of the muscular lacuna, from which latter the iliopsoas muscle has been removed, but in which the femoral nerve remains intact. Fig. 2b. The investing sleeves of the fascia have been cut away in such a manner as to reveal the muscles and associated structures which bound the femoral triangle. Marginally the triangular space is bounded by the sartorius and adductor longus muscles; the floor is formed in part by the pectineus muscle. The iliopsoas, removed from the muscular lacuna together with the subjacent portion of the articular capsule, would form the floor of the space laterally. The roof is the inguinal ligament. The stumps of the transected femoral vessels remain in the vascular lacuna. The small orifice situated on the medial aspect of the femoral vein is the femoral ring through which a hernia would pass from the abdomen into the thigh in the direction of the arrow *B*, to occupy the fossa ovalis. The hernia would be surrounded by the lamellae of the femoral sheath and would lie beneath the superficial fascia (see following dissections continued in specimen II).

of course, only after investing tissues, related to the blood vessels, have been removed. These tissues form coverings for the vessels, and would likewise invest a neighboring hernia, in the most medial of the three spaces of the vascular lacuna. This medial space is the femoral canal; its orifice beneath the inguinal ligament is the femoral ring.

The two investments of a femoral hernia are derived from abdominopelvic layers. The outer layer is a femoral prolongation of the fascial coverings of parietal muscles, namely, transversus abdominis and iliopsoas (Fig. 3d). They are carried outward to ensheath the femoral continuations of the external iliac vessels and as the wall of the femoral canal (arrow *B* in Fig. 3d). The inner coat is a derivative of the retroperitoneal (subserous) layer of the abdomen and pelvis (** in Fig. 3a, removed in Fig. 3d).

Internal to the subserous layer, in the abdomen and pelvis, is the peritoneum (freed and lifted in Fig. 3a). It would be the immediate covering of the herniating intestine or omentum.

Obviously, then, as a hernial protuberance is exposed by incision through the skin, it consists of the following from without inward: the superficial fascia of the thigh, with contained vessels and nerves; the outer femoral sheath (from the internal investing fascia of the abdominal and pelvic musculature); the inner sheath (from the retroperitoneal layer); the serous coat (as a diverticular process of the peritoneum over the femoral ring); space (continuous with that of the peritoneal cavity); the hernia itself.

The several layers, their thickened portions and the orifices, or faults within them, will now be considered from without inward, in the order in which they would be encountered in dissection.

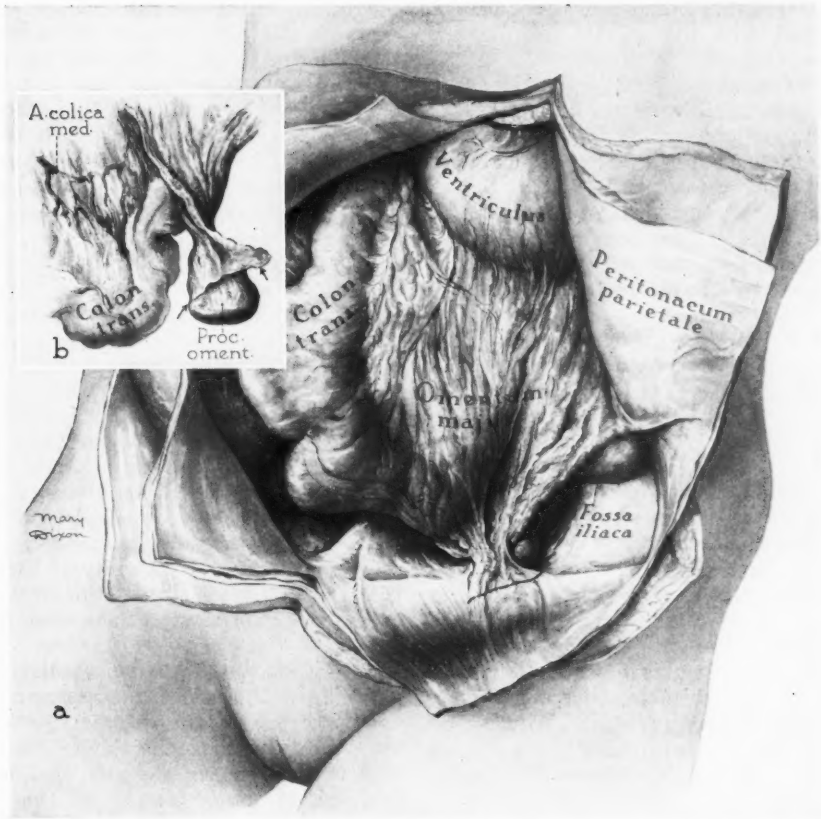
1. *Skin and superficial fascia.* The outer layer of superficial fascia of the abdomen (Camper's layer) is continued downward into the thigh, over the inguinal ligament. It contains moderately large lobules of fat and vessels of small size. In the region where the hernial mass protrudes, the layer of superficial fascia is thinned and the fatty tissue almost disappears.

The deep layer of superficial fascia in the inguinal region is a membranous sheet, irregularly bound down to the subjacent fascia of the external oblique muscle. This layer (Scarpa's fascia) finds a firm attachment along a line just below and parallel to the inguinal ligament and, thereby, to the fascia lata. Distal to the level of the ligament, Scarpa's layer immediately thickens to accommodate a considerable quantity of fatty tissue, superficial arteries and veins, and lymphatic vessels and glands. The thickened portion of the deep layer extends downward for a distance of a few centimeters beyond the inguinal ligament. Laterally, medially, and inferiorly, beyond the boundaries of the femoral triangle, the layer thins to become indistinguishable from a fatty pannicle. The inguinal lymph glands, the main portions of the superficial arteries and veins, emanating from and converging upon the fossa ovalis, lie chiefly within this deeper lamella.

Since the hernial mass regularly gains an external position by issuing through the upper part of the fossa ovalis, it must here encounter the deep layer of the superficial fascia. As the hernia increases in size, its shape and position are seemingly determined by the firm marginal attachments of the layer, and by its contents (see hereinafter).

2. *Fascia lata and fossa ovalis.* The thick sheath (fascia lata) for the muscles of the thigh is aponeurotic rather than fascial. It is anchored to the inguinal ligament, and, indirectly, to the underlying iliopsoas muscle-fascia, since the latter gives partial origin to the inguinal ligament (Figs. 1a to 1f).

The oval defect in this investing sleeve, namely, the fossa ovalis, is so placed that medially and superiorly a narrowed strip, a so called superior cornu, is formed. The cornu is carried inferomedialward, in a falciform margin, to become continuous with the pectineal fascia on the floor of the fossa, and with the lacunar extension of the inguinal ligament. In being so disposed, the free edge of the superior cornu completely hides the lacunar ligament in external view. The superior cornu, in being prolonged downward as a falciform margin of the fossa, ends medially in an inferior cornu. The inferior cornu, then



Figs. 4a and 4b. Abdominal contents in a case of femoral hernia in a female cadaver. Specimen IV. Fig. 4a. The omentum, with the transverse colon at its distal margin, forms an apron which almost completely obscures the coils of intestine. On the left side the omentum is locally fastened by a narrow band (along broken line) to the abdominal wall over the roof of the femoral canal. A nodule of the omentum occupies the femoral canal (orifice of the latter, 1 cm. in diameter). Fig. 4b. The hernial mass, removed from the femoral canal, has been turned upward to demonstrate its form and size. Prior to the time when removal was accomplished the omentum was cut (at arrows) from the area of anterior fixation to the parietal peritoneum (see Fig. 4a).

sweeping upward, becomes continuous with the pectineal fascia on the floor of the fossa. The pectineal part lies at a deeper level than the more lateral and superior portions. Behind the femoral vessels it ascends, for attachment, to the superior ramus of the pubis, covering the pectineus muscle as it does so. The difference in level between the superior cornu of the fossa and the upper attachments of pectineal fascia accounts for the depth of the vascular lacuna which, in transmitting the femoral artery and vein, contains a compartment for each of these vessels as well as a third space, termed the femoral canal (Figs. 2a and 2b at arrows *B*). It is in the last-named division of the lacuna that the neck of a femoral hernia sac is encountered.

Based upon a study of 200 specimens, variations in form and size of the fossa ovalis may be described and figured. In outline, the fossa is occasionally almost circular (Fig. 1a). Usually, however, it is oval (Fig. 1d); when thus compressed laterally, the long axis may be placed vertically (Fig. 1c), or ob-

liquely (Fig. 1e). Occasionally the fossa is dart-shaped, with the pointed end directed downward (Fig. 1f).

The relationship between the superior cornu and the inguinal ligament is inconstant. It is conventionally described as being attached above to the medial half of the inguinal ligament. When the fossa is proximally placed in the thigh, the superior horn appears to be a derivative of the inguinal ligament (Fig. 1b), the ligament itself seeming to serve as one boundary of the fossa. Its independence in other instances is equally striking, an appreciable distance often intervening between the ligament and the cornu (Figs. 1a, 1c to 1f).

Within the space of the fossa accessory hiatuses not infrequently occur, transmitting tributary veins from muscles to the femoral vein. These appear in simple form (Fig. 1c) or as multiple orifices (Fig. 1d).

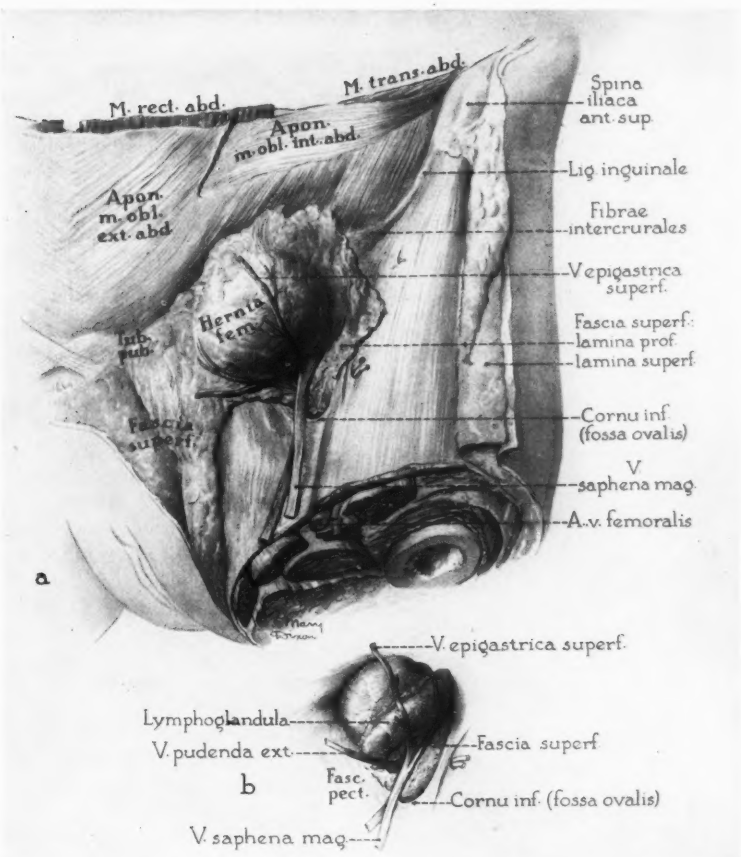
In size the greatest variability is encountered. The smallest fossa in the 200 specimens is 1.6 centimeters in length, 1.7 centimeters in width; the narrowest measures 1.0 centimeter, the shortest, 1.6 centimeters. The largest fossa in the group is 8.5 centimeters in length, 3.5 centimeters in width; the widest measures 6.4 centimeters, the longest, 8.5 centimeters. Ninety per cent of the specimens (i.e., 180 fossae) measure between 3.0 centimeters and 6.4 centimeters in length; 53.5 per cent (107 fossae) measure between 3.5 centimeters and 5.4 centimeters. The average length is 4.6 centimeters. In width, 87 per cent (174 fossae) are between 1.5 centimeters and 3.9 centimeters; 70.5 per cent (141 fossae) are between 2.0 centimeters and 3.9 centimeters.

Without exception fossae are capacious orifices for the vessels which they transmit; in only one case does the circumference of the saphenous vein approach that of the fossa through which it passes; regularly a very considerable space, unoccupied by vessels, is included between the cornua of the fossa (e.g., Figs. 1c to 1f), the size of contents in no way affecting the proportions of the orifice. So ample, in fact, is the space of the fossa, that the contained femoral vein is almost invariably exposed throughout its width. Moreover, in 83 per cent of 100 consecutive cases the femoral artery, also, is wholly or partially exposed. More specifically, in 36 per cent, three-fourths to all of its breadth is in view (Fig. 1e); in 30 per cent, one-half to one-fourth; in 17 per cent, not only is the artery entirely in view, but space occurs laterally, unoccupied by vessels (Fig. 1b).[1] It might be safely assumed that capaciousness of space would render hernial migration easier.

In the hernial specimen illustrated, the fossa is elongate (Figs. 5a and 5b). The neck of the hernial sac impinges medially upon the free edge of the superior cornu. Behind, it rests upon pectineal fascia. The hernia thus lies anterior to the confluence of saphenous and femoral veins in the fossa ovalis; superficial veins enter the saphenous behind and below the body sac; the external pudendal vessels course across the fossa ovalis below the sac, while the superficial epigastric artery ascends from the region of the fossa lateral thereto (Fig. 5b). Superficial lymphatics which ascend from the lower extremity and from adjacent lymph glands pass into the vascular lacuna posterior to the body and neck of the sac.

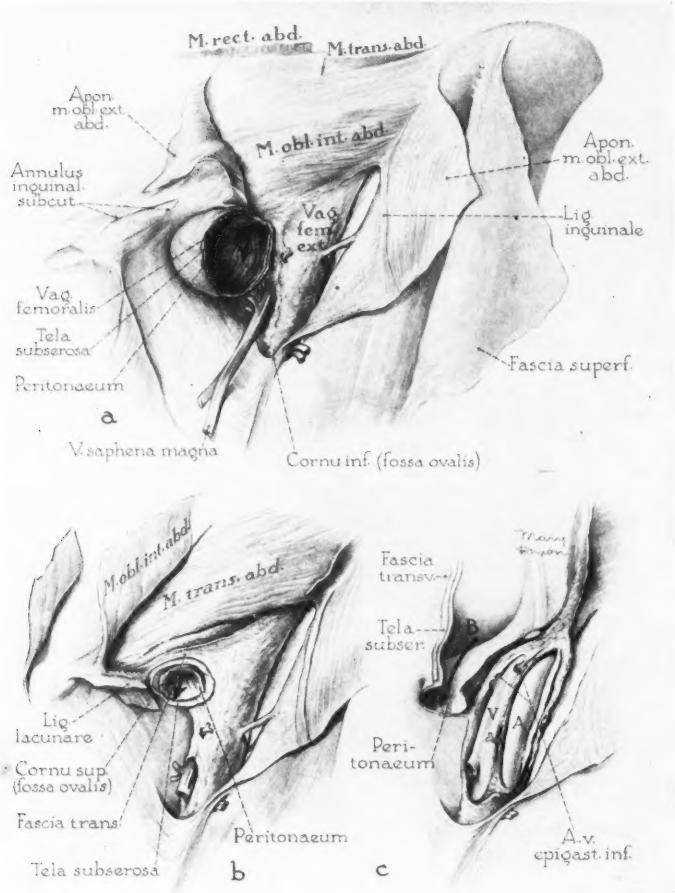
3. *External femoral sheath.* At the inguinopelvic interval, a space, the vascular lacuna, permits egress of the external iliac vessels from the pelvis into the thigh. The orifice thus produced is an elongate oval with its long axis in transverse plane. The lacunar ligament, the inguinal ligament, the iliopsoas muscle, and the superior ramus of the pubis form the resistant boundaries of the orifice. Internal to these structures the iliac fascia of the pelvis and that of the inguinal wall (transversalis fascia), are carried in a femoral direction around the margins of the orifice, to produce an infundibuliform investment for the femoral vessels. Anteriorly and medially this fascial funnel is supported from without by the lowermost aponeuroticofascial portions of the transverse abdominal and internal oblique muscles. These strata arise partly from the medial edge of the iliopsoas fascia in common with the inguinal ligament;

[1] The venous channels which converge upon the terminal segment of the great saphenous vein are highly variable. They have been described and figured in an article (based upon 550 specimens) by the present author and his colleagues in an earlier issue of this journal (1946, 82: 52–63).



Figs. 5a and 5b. The femoral hernia, in relation to the external fascial and aponeurotic layers of the inguinal and proximal femoral regions (same specimen). Fig. 5a. The superficial fascia has been removed except in the territory of the hernia and in the pudendal area medial thereto. The aponeurosis of the external oblique muscle and the fascia lata are shown. The fossa ovalis in the latter layer is exposed (for purposes of topography) in its lower part, that is, over the inferior horn of the falciform margin. The hernia produces a circular bulging in the overlying superficial fascia. In this fascia the superficial veins (pudendal, epigastric, circumflex iliac) descend to join the saphenous. Fig. 5b. The hernial sac in relation to the superficial veins and the falciform margin of the fossa ovalis. The superficial fascia has been removed from the hernial sac to reveal the latter's outline, a gland of the superficial subinguinal group, and the superficial veins. The veins form a basket-like support for the hernia, the latter being pressed upward against the inguinal ligament, not downward over the inferior cornu of the fossa.

they arch over the femoral vessels and gain a strong medial anchorage by their insertion into the pecten of the pubis behind the lacunar ligament. Thus the femoral sheath anteriorly is a fascial prolongation of the intermediate and innermost of the three muscle strata of the abdomen. Both medially and laterally at the femoral orifice the anterior part of the femoral sheath is continuous with a posterior component which consists of the iliopsoas fascia. While the lateral wall of the funnel-shaped femoral sheath is almost vertical, the medial wall describes a moderate curve, the concavity of which is directed medialward (see esp. Fig. 6b). Owing to the obliquity of the medial wall, as it extends from behind the lacunar ligament to reach the medial surface of the femoral vein, there exists



Figs. 6a to 6c. The hernial sac; its composition and inguinofemoral continuities (same specimen). Fig. 6a. The aponeurosis of the external oblique muscle has been reflected; with it the fascia lata has been turned aside after cutting vertically through the superior cornu of the falciform margin of the fossa ovalis. The lateral wall of the sac has been cut away. In this way the following features are demonstrated: the laminar nature of the hernial sac, derived in part from the femoral sheath; the relation of the orifice (at arrow) to the part of the sheath which invests the femoral vessels; the form and position of the sheath. The sac is composed of three layers, namely, the fascia of the abdominal and pelvic muscles, the subserous connective tissue, and the peritoneum. The femoral sheath is made up of the outer and intermediate of these three layers. Fig. 6b. The orifice of the hernial sac in relation to the deep inguinal and femoral structures. The sac has been transected at its neck; the internal oblique muscle has been turned aside to expose the subjacent transversus abdominis. As the sac passes through the femoral canal, it is bounded medially by the lacunar ligament (here cut and turned downward), laterally by the portion of the femoral sheath which transmits the femoral vein, superiorly by the lower margins of the three lateral abdominal muscles, and inferiorly by the superior ramus of the pubis (covered by the pectineus muscle and the pectineal fascia). The outer lamella of the femoral sheath is made up of the fascial coverings of the transversus and iliopsoas muscles prolonged into the thigh. Its surface (here exposed) is irregular, owing to the presence of fat in the contiguous layer of connective tissue. The latter, carried into the thigh as an extension of preperitoneal tissue in the pelvis, forms the internal layer of the femoral sheath and immediately surrounds the vessels (exposed in Fig. 6c). Fig. 6c. The compartments of the femoral sheath, their investments, contents and interrelationship. The hernial sac, in the medial one of the three compartments, has been opened in front, its constituent layers demonstrated by carrying the incision vertically upward through the deep layers of the inguinal wall. Its space (traversed by arrow *B*) is continuous with that of the peritoneal cavity. The bi-

(*Legend continued on opposite page.*)

a small, conical space within the sheath adjacent to the femoral vein. The base of the cone lies over the pubic pecten; the opening into the space is the femoral ring.

The lower aponeurotic and fascial portions of the internal oblique and transverse abdominal muscles cover the internal surface of the lacunar ligament by inserting into the pecten of the pubis; they form the immediate boundary for the femoral ring on its medial aspect. This "internal lacunar ligament" is strengthened by a flattened, aponeurotic, lateral expansion of the rectus tendon, which is fastened, with the transversus aponeurosis, to the superior pubic (Cooper's) ligament. The rectus margin is variable, since the tendon may be wide or narrow.

In the hernial specimens, while the anterior femoral sheath remains intact over the vessels, that part of the sheath once enclosing the canal medial to the femoral vein is greatly distended to form a thin envelope for the body and neck of the hernia (Figs. 6a to 6c). Since anteriorly the femoral sheath is made up of fascial continuities derived from the intermediate and deep muscular layers of the inguinal wall, the lowermost portions of these layers form an arch over the neck of the sac, strong when the layers are muscular or aponeurotic (Figs. 6a and 6b), weak when they are fascial. Posteriorly the femoral ring possesses, for firmer support, a wall consisting of the pectineus muscle and its investing fascia, and the superior ramus of the pubis (Fig. 6c; compare Figs. 3a and 3d). Laterally the neck of the sac is related to the femoral vein (Figs. 6b and 6c; compare Figs. 3a and 3b), separated therefrom by a thin cushion of adipose tissue in which are lodged lymphatic vessels.

4. *Internal femoral sheath and preperitoneal connective tissue.* The covering of the femoral vessels which is, as just described, derived from abdominal and pelvic fasciae, constitutes the femoral sheath of all regular, and therefore, familiar, textbook accounts. Actually, the vessels are imbedded in fatty connective tissue, which provides for them a second, or internal, femoral sheath. This matrix is directly continuous with the preperitoneal tissue layer of the abdomen; it surrounds, and passes as septal walls between, the femoral artery and vein; it fills the conical femoral canal (Figs. 3a to 3c), and conveys lymphatic channels from the inguinal to the iliac lymph glands.

As seen from the abdominal aspect, the external iliac vessels course toward the lateral and intermediate portions of the vascular lacuna (Fig. 6c; compare Figs. 2b and 3a). The femoral canal, in the medial part of the lacuna, is normally filled with fatty preperitoneal (retroperitoneal, subserous) connective tissue. This tissue conceals the pelvic opening or "ring" of the femoral canal, but leaves a concave depression on which the peritoneum rests. This concavity is the femoral fossa. It is this point at which a hernia initially presses the peritoneum into the subjacent femoral ring. In specimens of femoral hernia this preperitoneal layer forms an important envelope for the hernial process (Figs. 6a to 6c).

In the preperitoneal connective tissue of the lower abdominal wall the inferior epigastric vessels course obliquely from the femoral sheath to the rectus muscle (Fig. 3a). However, an anomalous branch, the obturator artery, in approximately 30 per cent of cases, descends medially, in arciform course, close to the femoral ring. The umbilical artery passes upward in the lateral umbilical fold 0.5 to 1.0 centimeter medial to the femoral ring. Supposedly obliterated, this vessel sends small branches forward, beside the urinary bladder; they pass over the pubic pecten and into the femoral ring, to form an additional supply for the tissue within and about the femoral canal.

5. *Peritoneum.* A slight peritoneal depression, or femoral fossa, marks the site of the femoral ring. It is critically located at the abdominopelvic junction. This small fovea in the serous layer rests below upon the rounded margin of the pubic pecten and the origin of the pectineus muscle. Medially is situated the lateral umbilical fold—a fairly tall plica

laminar sheath, which houses the femoral vessels, has been opened to demonstrate the continuity of its strata with those of the abdomen. The hernial sac is thus a diverticulum of the parietal peritoneum which, covered by subserous and fascial coats, presses outward through the vascular lacuna beneath the inguinal ligament to occupy a once "empty" compartment of the femoral sheath.

in the majority of cases. Laterally lies the peritoneal elevation for the epigastric vessels; usually this fold is low. The femoral fossa, therefore, lies at the inferomedial edge of the medial inguinal fossa, and is so placed as to be the apex of a broad peritoneal funnel, toward which apical point the vertical wall of the lateral umbilical fold might assist in directing a mobile viscus or a portion of the omentum. The peritoneum which forms the femoral fossa, together with the subjacent preperitoneal tissue, becomes protuberant over the herniating mass (Fig. 6a). External to the subserous coat is the fascial envelope derived from the transversus abdominis and iliopsoas muscles (Figs. 6a to 6c; compare Fig. 3a, layer marked 3). This outer coat is the femoral sheath of familiar descriptions (the inner, subserous investment customarily being disregarded). In further excursion, a portion of jejunoileum, or of omentum (Figs. 4a and 4b), descending through the femoral canal, gains a fourth covering, the superficial fascia of the thigh (Figs. 5a and 5b); this pannicle becomes a hernial coat as soon as the hernia reaches the fossa ovalis. Thereupon, the hernia acquires relationships to superficial blood vessels, lymphatics, and cutaneous nerves regularly present in the superficial fascia of the femoral triangle and in the corresponding stratum of the inguinal region (Figs. 5a and 5b, 1a to 1f). The veins which converge upon the saphenous and femoral may, apparently, be instrumental in directing the hernia cranialward, over the inguinal ligament (Fig. 5a). In the specimen illustrated, the course was initially downward and forward (Figs. 6b and 6c, arrows *B*), then somewhat upward (Figs. 5a and 5b).

The solidity of the floor beneath the femoral ring is another feature of anatomical and surgical significance. Outside the peritoneum and preperitoneal connective tissue lies the bony ridge of the pubic pecten. From this ridge the superior surface of the pubic bone slopes slightly downward and forward, covered at the more distal portion by the pectineal fascia and muscle. It is this declinated surface which forms the actual floor of the ring and canal, and, therefore, a guide for the hernia in the first stage of its emergence.

CONCLUSIONS

On the internal aspect, the abdominal wall presents an oval fovea corresponding in position to the femoral ring. Here, as elsewhere, the peritoneum of the fovea rests upon a stratum of connective, the preperitoneal, tissue. Externally, both on the abdomen and in the proximal thigh, the superficial fascia is bilaminar in character. The deeper portion is locally thickened through inclusion of fat, subcutaneous vessels and lymph glands. As the subserous tissue is prolonged upon the femoral continuations of the external iliac vessels, it is in turn covered by fascia derived from the parietal musculature. These are, respectively, inner and outer lamellae of the femoral sheath. They are carried downward through the vascular lacuna (beneath the inguinal ligament), to lie deep to the superficial fascia of the thigh where the fault in the investing fascia (fascia lata) brings them into contact. The same relations are acquired by any herniating mass which, coming to occupy the most medially situated space in the femoral sheath—namely, the femoral canal—passes in succession through the femoral ring, femoral canal and fossa ovalis, to subcutaneous position.

The pathway taken by a femoral hernia, then, must be at first almost directly downward into the femoral fossa, declination of the superior surface of the pubic bone carrying the process forward through the femoral ring. The herniating structures meet a restraining arch of aponeurotic fibers formed by that part of the femoral sheath which is securely attached to the pubic pecten. Further resistance is offered by the lacunar ligament. But within the vascular lacuna the femoral vein and the investing sheath constitute a resilient lateral wall. Further progress distalward brings the process into the lower reaches of the femoral canal, where it impinges upon the overlying superior cornu of the fossa ovalis. After passing this point, the process is suddenly relieved of anterior constriction, and can press toward the integument in angulated course. While the neck of the process must remain small in size, the distal mass of the tumor may thus increase in bulk. In this situation, carrying the bilaminar femoral

sheath forward as a conjoined envelope, the hernia impinges upon the deep layer of the superficial fascia, as the latter locally covers the fossa ovalis. Further descent is seemingly hindered by the basket-like arrangement of vessels related to the fossa, and by marginal fixation of the cribriform layer. The hernia consequently presses superiorly in front of the falciform margin and over the inguinal ligament.

Considering anterior hernial orifices together, the femoral canal (with the ring) represents an anatomical arrangement standing between inguinal and obturator canals in point of structural weakness.

Tendency toward hernial protrusion through the inguinal wall is greatly increased by the presence of a congenital serous sac, and by subjection to the trauma and intra-abdominal pressure against parietes which are distensible. The femoral orifice is a narrow one, encircled in front by an aponeurotic arch, bounded by the lacunar ligament medially, and supported behind by a bony ridge. It is weakened only by the existence of potential space in the femoral ring and canal, and by resilience of the large blood vessels on its medial aspect. As will be seen, the obturator orifice, narrower still, is effectively bounded by an osseoligamentous rim, the obturator canal; the canal not only possesses peritoneal, preperitoneal, and ligamentous tissues to support it internally, but also is well barricaded externally by the layered musculature of the thigh.

In a succeeding, and final, paper in this trilogy, the anatomy of obturator hernia will be considered.

OBSERVATIONS ON THE CLOTTING MECHANISM IN MENSTRUATION AND MENORRHAGIA

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IN certain diseases complicated by hemorrhage the whole blood clotting time may be prolonged and an abnormality can be detected by a protamine titration (2). Increases in the protamine titration and whole blood clotting time may occur when all other known hemostatic mechanisms are normal, although usually these changes are associated with some degree of thrombocytopenia (1).

Bleeding in such individuals may be temporarily controlled, partially or completely, by the administration of adequate amounts of toluidine blue and protamine sulfate. These agents are known to inhibit heparin and heparin-like substances. The fact that such patients respond to these antiheparin agents (toluidine blue and protamine sulfate) suggests that the clotting defects may resemble that produced by the intravenous injection of commercial beef heparin (3). This comparison, however, may not be valid because certain other endogenous compounds having heparin-like action appear to be chemically different from heparin. Also, it is possible that this physicochemical change only resembles that produced by heparin, and that it is accomplished by a mechanism unrelated to heparin (3).

Menorrhagia was among the bleeding conditions investigated. This study includes coagulation data on 43 patients with menorrhagia, 23 normal female volunteers and 56 normal males.

METHOD OF STUDY

Gynecologic examination of the menorrhagic group was performed by one of us (A.K.K.) and, except for 2 patients who had small uterine fibroids, no gross pelvic disease was found. Biopsies on the first day of menstruation revealed no characteristic endometrial pattern. The diagnosis of menorrhagia was based on a history of prolonged profuse menstrual bleeding and anemia. The normal females consisted of volunteers carefully studied with reference to their menstrual history and blood findings. Pelvic examinations were not performed. The group constituting the normal males was composed of medical students and other hospital personnel.

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Laboratory studies in both the normal and the menorrhagic groups included: the protamine titration (2); whole blood clotting time (4); prothrombin time (5); gross observations for lysis of clots; clot retraction at 1, 6, and 24 hours; and, platelet count. There was no evidence of a blood dyscrasia in any of the patients. The menstrual blood was not examined.

These studies were carried out at different intervals during the menstrual cycle and on the day of heaviest menstrual flow. This usually was the second day of the menstrual bleeding.

Protamine sulfate was administered as a single intramuscular injection of 50 milligrams, usually on the day of heaviest flow. Toluidine blue was given orally twice daily for 3 to 4 days in capsules containing 100 milligrams, beginning on the heaviest day of flow.

DATA

Table I presents the results of the protamine titration, the whole blood clotting time, and the group average platelet count in the menorrhagic patients and in the normal female and male groups. The determinations on the menorrhagic group were made during menstrual periods before protamine sulfate or toluidine blue were given.

In Table II are summarized data obtained on patients in the menorrhagic group when protamine sulfate was given intramuscularly

TABLE I.—RESULTS OF THE PROTAMINE TITRATION, THE WHOLE BLOOD CLOTTING TIME AND PLATELET COUNT IN THE MENORRHAGIC AND THE NORMAL GROUP

No. determinations	When performed	Protamine titration		Whole blood clotting time*		Average platelet counts
		Increased	Normal	Increased	Normal	
43 Menorrhagic Patients						
106	During profuse menstruation	80	26	62	45	166,000
14	During normal menstruation	3	11	7	7	183,000
82	Intermenstrually	39	43	41	36	193,000
23 Normal Women						
23	During menstruation	5	18	13	10	236,000
35	Intermenstrually	11	24	14	21	211,000
56 Normal Males						
105		3	102	10	95	230,000

*By the technique employed the normal whole blood clotting time ranged from 25 to 35 minutes (4)

TABLE II.—BLOOD STUDIES AND CHARACTER OF MENSTRUATION IN PATIENTS WITH MENORRHAGIA GIVEN PROTAMINE SULFATE OR TOLUIDINE BLUE

Results in 32 patients given protamine†			Studies before administration of protamine			
			Protamine titration		Whole blood clotting time	
Effect*	No. of periods	No. of patients†	Increased	Normal	Increased	Normal
Good	30	25	27	3	19	11
Temporary	5	5	3	2	2	3
None	7	7	3	4	3	4
Results in 12 patients given toluidine blue††			**Studies before administration of toluidine blue**			
Good	7	6	4	3	5	2
Temporary	5	5	4	1	1	4
None	3	3	1	2	0	3

*Good effect—Reversion from profuse to normal menstrual flow for remainder of period
Temporary effect—Bleeding slowed 6 to 18 hours, profuse bleeding resumed
No effect—No detectable improvement
†Seven patients were given protamine sulfate during 2 or more menstrual periods
††Three patients received oral toluidine blue during 2 or more menstrual periods. Nine patients had received protamine sulfate during previous menstrual periods

or when toluidine blue was administered orally.

Gross fibrinolytic activity was noted in only 1 patient. Prothrombin activity was within normal limits in all bloods studied. Prothrombin accelerator factors were not determined.

COMMENT

Several changes referable to the clotting mechanism have been reported for venous blood during the menstrual cycle. Among the changes noted have been a slight increase in the whole blood clotting time (7), a mild to moderate thrombocytopenia (8), and alterations in fibrinolytic activity (6). Many of the patients in our study developed some degree of thrombocytopenia and a slight to moderate increase in the whole blood clotting time during menstruation. These changes occurred also during the intermenstrual period in several members of both the normal and the menorrhagic groups, although less often and less extensively. The increased clotting times were detected only when careful techniques were employed (4).

The abnormality revealed by the protamine titration appeared to be a better index of a systemic hemostatic disturbance in these patients than was either the whole blood clotting time or the platelet count. The protamine titration was increased in 80 of 106 determinations made during menorrhagic periods. It increased in only 5 of 23 determinations made during menstruation in the women whose menses were considered normal (Table I). When increases in the titration occurred in the latter group, they were less pronounced than those in menorrhagia.

The response of those patients given intramuscular protamine injections correlated fairly well with the status of their protamine titrations at the time the injections were made. Listed as "good effect" in Table II are 30 responses, 27 of which were obtained when the titration was increased. Temporary or no effect was obtained in 12 menstrual periods, of which 6 were associated with increased protamine titrations. The response to oral toluidine blue was not impressive but the number of patients so treated was too small to evaluate.

The response of many of the patients with menorrhagia to a single intramuscular injection of protamine is difficult to explain, in that the duration of intramuscular protamine action is probably less than 4 hours (4). Most

patients who reported a reversion from profuse to normal flow remained normal for the rest of the menstrual period. These results were obtained when protamine was given intramuscularly on the second or third day of flow. This generally was coincident with an increase in the protamine titration and the onset of profuse bleeding. Temporary or poor results occurred most frequently when protamine was given on the first day of menstruation, even though in some patients the titration was increased at this time.

The mechanisms involved in menstruation and menorrhagia are not well understood and the nature of the systemic change responsible for the protamine titratable abnormality in the blood of these patients is even more obscure. Hence, these data cannot be interpreted with reference to the physiology of menstruation or coagulation. The fact that many of these patients appeared to respond to protamine sulfate is not in itself sufficient to conclude that the systemic blood disturbance in menorrhagia is the same as that produced by the injection of commercial beef heparin.

Therapeutic measures in menstrual disorders often can only be evaluated in terms of subjective descriptions by the patient. The difficulty in evaluation is further complicated by the fact that not all menstrual periods in women with menorrhagia are abnormal. Hence, a much larger series of normal women and patients with menorrhagia, studied with reference to their protamine titrations and response to intramuscular protamine injections and oral toluidine blue, will be required to estimate the therapeutic possibilities of these agents accurately.

SUMMARY

1. The presence of protamine titratable abnormality was observed at the time of menstruation. This abnormality was seen more commonly and more extensively in the 43 women with menorrhagia than in the 23 whose menstrual periods were normal.

2. Many patients also had a prolonged whole blood clotting time and a mild to moderate thrombocytopenia. Prothrombin activities were essentially normal. Gross evidence of fibrinolysin was observed in only 1 patient.

3. The blood studies and clinical courses following the administration of protamine sulfate or toluidine blue in a group of 34 women with menorrhagia are presented.

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MULTIPLE PRIMARY CANCER

A Study of Thirty-six Patients

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IN spite of the fact that tremendous advances have been made in the fields of cancer research and the related sciences since Billroth first reported the occurrence of multiple primary malignant neoplastic disease nearly 80 years ago, the true biological significance of this condition remains obscure. Final clarification depends primarily on the correct explanation and evaluation of the various extrinsic and intrinsic factors that initiate and control malignant anaplastic cytological changes and secondarily on the statistical contributions of clinical medicine. Ewing has stated that "the study of the conditions under which cancer develops belongs to clinical medicine and pathology, while the investigation of the cell processes calls upon all of the fundamental medical sciences." With this in mind, and prompted by the fact that an increasing number of cancer patients seen in the Department of Surgery at Harper Hospital were observed to have been afflicted with a second primary malignant lesion, we made the following résumé of current thought on the subject with a report of 36 cases.

MODE OF ORIGIN

As reliable scientific data have accumulated, the theory of unicentric origin, which holds that neoplastic processes develop exclusively from a single cytologic focus, has gradually given way to the theory of multicentric origin. The latter proposes that neoplastic transition may occur independently at two or more isolated points, either simultaneously or at variable intervals, thus producing independent multiple lesions or solitary lesions by the coalescence of adjacent foci.

In an excellent review of the subject, Slaughter discusses the following evidence favoring the multicentric origin of both benign and malignant tumors. Examples of the former include pigmented nevi, keratotic warts, lipomas, neurofibromas (von Recklinghausen's disease), papillomas of the urinary bladder, multiple polyps of the stomach and colon, and fibromyomas of the uterus. Examples of malignant neoplastic disease of diffuse origin include the leucemias, Hodgkin's disease, and idiopathic multiple hemorrhagic sarcoma (Kaposi's disease). Multiple myeloma has also been cited as an example, but the mode of origin of this disease is subject to question. Brill Symmer's disease (giant follicular lymphadenoma) is regarded by some investigators as a precursor of lymphosarcoma.

Microscopic evidence of the multicentric origin of malignant neoplastic disease is commonly found in lesions such as intraepithelial epidermoid "carcinoma in situ" (Bowen's disease) and in the malignant degeneration of widely separated polyps of the colon. "Carcinoma in situ" has been demonstrated in skin, cervix, larynx, and other organs by Broders (28), in the breasts by Foote and Stewart (28), and by Mallory (28) in the gastric mucosa. Ewing has stated that "precancerous" or preinvasive anaplastic cytological changes can be demonstrated in areas outside of the limits of the frankly invading carcinoma.

Although this evidence does not conclusively prove the multicentric origin of multiple neoplastic disease, or exclude the possibility of unicentric origin, it offers tangible evidence that isolated anaplastic cellular changes do occur.

INCIDENCE

The incidence of carcinoma based on postmortem findings at Wisconsin General Hospital (University of Wisconsin) (7), University Hospital (University of Michigan) (7), and

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TABLE I.—REPORTED INCIDENCE OF MULTIPLE PRIMARY MALIGNANT TUMORS

Source	Rate per cent
Second Budapest Pathological Hospital (7)	0.3
University of Milan (7)	0.5
Erisman General Hospital, Leningrad (7)	1.87
Schreiner and Wehr	2.7
Hurt and Broders	3.34
Lichtman	3.50
Warren and Gates (32)	3.70
Stalker, Phillips, and Pemberton	4.52
Berson and Berger	4.60
Owen	4.70
Warren (31)	6.00
Warren and Erhenreich (27)	6.8
United States Average (32)	3.90
Combined European and United States Average (32)	1.84

the Mayo Clinic (7) averages about 30 per cent of autopsies. Warren and Gates (32) report an incidence of 13.8 per cent based on a review of 115,813 postmortem examinations.

The incidence of multiple primary malignant neoplasms has been variously reported between 0.3 and 6.8 per cent of all cancer cases as shown in Table I.

AGE AND SEX

The average age of occurrence of multiple primary malignant tumors varies, according to the literature, between 50.4 and 62.1 years. Insufficient data have accumulated to distinguish any significant correlation between age and multiplicity of lesions.

Available statistics regarding the incidence in the two sexes are inconclusive; however, they seem to indicate a slightly higher incidence in males.

SUSCEPTIBILITY, IMMUNITY, AND HEREDITY FACTORS

Computations by Bugher based on cancer statistics of the United States during the period 1920 to 1928 indicated that the actual incidence of multiple primary neoplastic disease is greater than can be expected on the basis of chance alone.

The preponderance of opinion seems to favor a tumor diathesis or susceptibility factor in a certain percentage of the population; however, Ewing, Hanlon, and Seecof (16) have suggested that the incidence is compatible with the accidental rate. Ewing states that "the validity of assuming the existence of a predisposition to cancer based on current available statistics is subject to doubt. So many events of widely separated significance have been included in the reports of multiple malignancies that no definite conclusions can be drawn. Multiple malignancy is an accidental coincidence of the biological factors in the incidence of tumors. . . . Clinical studies indicate that there is, among human beings, a general susceptibility to tumors, but as a rule, the susceptibility is negligible and the disease is not developed until the real affective causes of the disease are brought into play."

In the statistics available, approximately 26 to 29 per cent of patients with multiple primary malignant tumors have a family history of cancer.

Until further evidence has accumulated, no definite conclusions can be drawn concerning the significance of the immunity, susceptibility, or heredity factors.

COMBINATIONS

The potential combinations of primary malignant tumors are numerous, but Slaughter has shown in his analysis of 1,868 cases that there is a striking tendency for them to occur in the same organ or in paired organs (54.3 per cent). This observation has also been made by Lichtman and Stalker, Phillips, and Pemberton. Ewing reported that bilateral primary carcinoma of the breasts occurs in 1.5 per cent of the cases. According to the literature, multiple primary neoplasms occur most frequently in the skin or in combinations with the skin. This group constitutes more than 50 per cent of the cases in many of the earlier reports. As Slaughter points out, the fact that the skin is the system most frequently involved is not surprising, when one considers the relative size of this organ and the frequency with which it is exposed to external chemical and physical carcinogenic stimuli. Schreiner and Wehr observed that basal cell carcinoma is found more frequently than squamous cell carcinoma in multiple primary tumors involving the skin.

The next most commonly involved system is the gastrointestinal tract, followed by the genitourinary system. According to Slaughter's work, the order of frequency of involve-

ment of the several divisions of the gastrointestinal tract is: colon, first; combinations of colon and stomach, second; and stomach, third, which, as he points out, is somewhat of a surprise as gastric carcinoma is not generally thought of as being multiple.

As would be expected, the highest incidence in the paired organs occurs in the breasts, ovaries, testicles, and kidneys in that order.

Multiple primary tumors involving two different systems occur most frequently in the gastrointestinal and genitourinary systems. Second in frequency are tumors involving the breasts and genitourinary tract.

Multiple sarcomas are relatively rare; however, combinations of carcinoma and sarcoma are not infrequent.

Certain combinations, particularly those involving the same tissue or same organ, are frequently difficult to prove because of the problem of excluding metastasis. Examples of these are multiple primary lesions confined to the ovaries, breasts, skin, colon, and combinations involving the ovaries and gastrointestinal tract (Kruckenberg). Teratomas also give rise to doubt in certain cases.

THE SIGNIFICANCE OF THE ENDOCRINE SYSTEM IN MULTIPLE PRIMARY NEOPLASMS OF PAIRED ORGANS

The existence of a relationship between the estrogenic hormones and carcinoma of the breast is generally accepted; however, the exact significance of this relationship is not clearly understood. It is well known that surgical castration following primary carcinoma of the breast frequently alters the course of the disease in patients in the premenopausal state.

Dockerty (4) states that granulosa cell and theca cell tumors occasionally produce adenocarcinoma of the breast and uterus as the result of a hormonal disturbance.

Slaughter has suggested that if carcinoma of the breast is a systemic disease predicated on an endocrine background, then the bilateral occurrence of breast cancer could be readily explained. Likewise, bilateral carcinoma of the ovaries and testicles could be explained on a similar basis rather than on the basis of chance alone.

CRITERIA FOR DIFFERENTIATING PRIMARY MALIGNANT NEOPLASTIC DISEASE

Billroth (32) proposed the following criteria which have generally been discarded because they were too strict: (1) the tumors must have a different histological appearance; (2) they must arise in different locations; and (3) they must each produce their own metastasis. The third postulate would obviously rule out many cases which are beyond reasonable doubt.

Goetze (15) revised Billroth's criteria slightly and proposed that: (1) each tumor must present the microscopic and macroscopic picture of the usual tumors involved; (2) the possibility of metastasis must be excluded with certainty; and (3) diagnosis must be confirmed by the character of the individual metastasis. As in Billroth's criteria, the third postulate falsely eliminates many true malignant primary neoplasms.

Dissatisfied with these, Warren and Gates (32) liberalized their criteria as follows: (1) each tumor must present a definite picture of malignancy; (2) each tumor must be distinct; and (3) the probability of one tumor being a metastasis of the other must be excluded.

Many reported cases have been disregarded in the statistical reviews in the literature because they did not conform to the criteria of the author concerned. Many others occurring in the same or paired organ or in the same or adjacent systems have been subject to question.

DISCUSSION OF STATISTICAL DATA

Early in the course of this investigation it was realized that the number of cases acceptable for this report would not be as large as expected because of the difficulty in proving that the second neoplasm concerned was an independent primary tumor rather than an extension of the original growth.

More than 60 per cent of the cases originally reviewed were discarded for one reason or another. The chief cause for elimination was due to the fact that clinical diagnosis of one or the other of the tumors had not been conclusively confirmed by histopathologic proof. Other cases were discarded when it was revealed by their histories that the original primary lesion had been diagnosed and treated

TABLE II.—PATIENTS WITH FAMILY HISTORY OF CANCER

Case No.	Case diagnosis	Family history
19	Carcinoma of breast and ovary	Mother died, carcinoma of stomach
22	Carcinoma of breast and cervix	Mother died, carcinoma of stomach
11	Carcinoma of sigmoid colon	Mother died, carcinoma of unknown site
9	Carcinoma of breast and stomach	Mother has carcinoma of breast
5	Carcinoma of rectum and colon	Father died, carcinoma of bladder
32	Sarcoma of nose and carcinoma of breast	Mother had carcinoma of uterus Grandfather died, carcinoma of stomach Two aunts died, carcinoma of unknown site
25	Carcinoma of breast and uterus	Father died, carcinoma of prostate Brother died, carcinoma of bowel Four sisters died, carcinoma of breast
27	Carcinoma of breast and uterus	Brother died, carcinoma of lip Brother died, carcinoma of liver

at some other institution. Still others were discarded because the lesions concerned were confined to paired organs (as the breasts, ovaries, and kidneys) and the possibility of metastasis could not be ruled out. In spite of the fact that a large percentage of the cases reviewed did not fulfill the requirements of the criteria used, it was felt that many of them represented true cases of multiple malignant primary tumors.

We have included in this report only those cases (1) which have been proved to be malignant tumors microscopically, (2) which presented the gross and microscopic characteristics of the usual primary neoplasms found in the organs involved, and (3) in which the possibility of the second tumor being a metastatic lesion has been excluded to our satisfaction.

Thirty-six cases were finally selected from the Harper Hospital records of the last 20 years. In this group, there were 71 primary lesions, including 63 carcinomas, 5 sarcomas, 2 malignant teratomas, 1 malignant endothelioma, and 2 cases of myelogenous leucemia. Thirty-two of the patients were female and 4 were male, which represents a higher proportional incidence in women than previously noted in the literature.

TABLE III.—MULTIPLE NEOPLASMS OF THE GASTROINTESTINAL TRACT

Case No.	Age years	Sex	Diagnosis	Interval	Diagnosis
4	47	F	Adenocarcinoma of sigmoid colon	4 yr. 7 mo.	Adenocarcinoma of transverse colon
5	59	M	Adenocarcinoma of rectum	8 yr. 6 mo.	Adenocarcinoma of transverse colon
6	40	F	Adenocarcinoma of transverse colon	6 yr. 9 mo.	Adenocarcinoma of sigmoid colon
7	50	F	Adenocarcinoma of cecum	10 yr.	Adenocarcinoma of sigmoid colon

The age at the time of diagnosis of the first primary lesion varied from 28 to 78 years, and averaged 52.0 years. The age at the time of onset of symptoms of the second primary also varied between 28 and 78 years, and averaged 54.9 years. The interval between the onset of symptoms and the time of diagnosis of each neoplasm was so short in the majority of cases that this factor was considered negligible in computing the time intervals between lesions. The interval between the time of diagnosis of the first primary and the onset of symptoms of the second primary lesion ranged from 0 to 14 years, and averaged 3.22 years.

A reliable family history was obtained in 30 of the 36 cases, and of this number, 8, or 26 per cent, had a positive history of malignant disease, as noted in Table II.

It is of interest to note that in Case 25 there was a high incidence of carcinoma of the breast in the family. In this small series, however, it is impossible to draw any conclusions regarding a familial susceptibility factor.

The cases herein reported have been grouped according to the systems and system combinations concerned. In the 4 cases in which the gastrointestinal system alone was involved, the tumors were confined to the colon and rectum and there was no evidence of multiple polyposis in any case (Table III). Several cases of synchronous multiple lesions of the large bowel were reviewed, but were discarded on the basis that metastasis could not be ruled out. The interval between the occurrence of the two lesions in this series is worthy of note, the average being 7 years and 4 months. Malignant lesions of the upper gastrointestinal

TABLE IV.—MULTIPLE NEOPLASMS OF THE GENITOURINARY TRACT

Case No.	Age years	Sex	Diagnosis	Interval	Diagnosis
1	51	F	Sarcoma of ovary	3 yr. 9 mo.	Adenocarcinoma of uterine fundus
2	49	F	Sarcoma of ovary	2 yr. 11 mo.	Squamous carcinoma of uterine cervix
3	52	F	Adenocarcinoma of ovary	8 mo.	Squamous carcinoma of uterine cervix

tract, which have frequently been reported in the literature, are conspicuously absent in this series. In only 1 of the cases reported was there a family history of cancer.

Three of the patients were found to have multiple neoplasms confined to the genitourinary system, as shown in Table IV. It is of interest to note that all of these are combinations of ovarian and uterine tumors in which the ovary became involved first. As previously indicated, this group may not represent the correct percentage involvement of this system because of the fact that multiple primary lesions confined to the ovaries were disregarded. None of these patients had a positive family history of malignant neoplastic disease.

The 6 cases of multiple primary neoplasms involving the breasts and gastrointestinal tract, shown in Table V, are of considerable interest. Fifty per cent, or 3 cases, are combinations of the rectosigmoid colon and ovaries in which the initial lesion occurred in the bowel. The possibility of Kruckenberg tumors and direct extensions of the initial lesion were ruled out to our satisfaction in these 3 cases; however, it is realized that they may be a subject of controversy. Several cases with similar combinations were discarded because these possibilities could not be reasonably excluded.

As previously noted in Table III, the time interval between the initial and subsequent primary lesions confined to the large bowel averaged 7 years and 4 months. In contrast to this, it is of interest to note that when the second primary lesion involved the ovary, the time interval was reduced to 7 months. Accordingly, the survival rates were markedly reduced.

TABLE V.—MULTIPLE NEOPLASMS OF THE GASTROINTESTINAL AND GENITOURINARY SYSTEMS

Case No.	Age years	Sex	Diagnosis	Interval	Diagnosis
11	44	F	Adenocarcinoma of rectosigmoid	2 mo.	Adenocarcinoma of ovary
12	56	F	Adenocarcinoma of uterine fundus	7 yr. 2 mo.	Adenocarcinoma of cecum
13	59	F	Hypernephroma of kidney	5 mo.	Adenocarcinoma of sigmoid colon
14	28	F	Adenocarcinoma of rectum	1 mo.	Adenocarcinoma of ovary
15	41	F	Adenocarcinoma of uterine fundus	14 yr.	Adenocarcinoma of colon
16	59	F	Adenocarcinoma of sigmoid colon	1 yr. 6 mo.	Papillary carcinoma of ovary

In our experience, this combination seems to have a much poorer prognosis for survival than other combinations. As previously noted, this observation seems clinically significant, regardless of whether the ovarian neoplasms are primary or metastatic, in that it raises the question of the advisability of castrating all female patients with carcinoma of the gastrointestinal tract at the time of initial resection.

For example, in Case 14, a 28 year old white female was found to have grossly normal ovaries at the time of operation for a fairly early carcinoma of the rectum (Miles operation). Because of the patient's age and desire to have another child, and the lack of evidence of metastasis or local extension of the neoplasm, the ovaries were not removed. Approximately 2 months later, this patient returned with a rapidly enlarging abdominal tumor which proved to be a papillary cystadenocarcinoma of the ovary. Eighteen months later the patient expired as the result of a generalized abdominal carcinomatosis. It seems reasonable to assume that her life would have been extended if the ovaries had been removed at the initial operation.

Eleven, or 30 per cent, of the cases included in this report were combinations of breast and reproductive organs, as indicated in Table VI. The average time interval between lesions in this group was 1.7 years. The ovaries were involved in 3 cases and the uterus (cervix) in

TABLE VI.—MULTIPLE NEOPLASMS OF THE BREAST AND GENITAL ORGANS

Case No.	Age years	Sex	Diagnosis	Interval	Diagnosis
17	44	F	Teratoma of ovary	None	Adenocarcinoma of breast
18	66	F	Carcinoma of breast	None	Carcinoma of uterus
19	44	F	Carcinoma of breast	4 yr. 4 mo.	Carcinoma of ovary
20	48	F	Scirrhous carcinoma of breast	1 yr.	Adenocarcinoma of uterine fundus
21	61	F	Adenocarcinoma of uterine fundus	None	Scirrhous carcinoma of breast
22	47	F	Carcinoma of breast	2 yr.	Carcinoma of cervix
23	45	F	Primary duct carcinoma of breast	1 yr. 6 mo.	Teratoma of ovary
24	54	F	Adenocarcinoma of breast	7 mo.	Carcinoma of cervix
25	56	F	Carcinoma of breast	4 yr. 6 mo.	Carcinoma of uterus
26	39	F	Carcinoma of breast	1 yr. 9 mo.	Carcinoma of uterus
27	44	F	Carcinoma of breast	4 yr. 4 mo.	Squamous carcinoma of cervix

the remaining 8. Two of the tumors involving the ovaries were teratomas.

Of this group, adequate histories were available in only 10 cases which revealed that 6 of the patients had passed the menopause at an average age of 50 years and the remaining 4 were between the ages of 44 and 47 years. Eighty per cent of this group were parous. Menstrual histories were essentially normal in all cases but 1.

In this small group, there is nothing to indicate endocrine imbalance, and the group as a whole falls well within the limits of normal with regard to menstrual history and fertility.

Table VII includes 3 cases in which one of the primary lesions occurred in the breast and the other in the gastrointestinal tract. Noteworthy only is the fact that all of the breast lesions were of the scirrhous variety.

The final category of multiple neoplasms is composed of miscellaneous combinations of lesions involving unrelated organs and systems. Table VIII indicates the nature and locations of these lesions.

Neoplasms involving the skin constitute only 8.3 per cent of this total series, which is

TABLE VII.—MULTIPLE NEOPLASMS OF THE BREAST AND GASTROINTESTINAL TRACT

Case No.	Age years	Sex	Diagnosis	Interval	Diagnosis
8	44	F	Adenocarcinoma of transverse colon	4 yr.	Scirrhous carcinoma of breast
9	49	F	Scirrhous carcinoma of breast	6 yr.	Scirrhous carcinoma of stomach
10	78	F	Scirrhous carcinoma of breast	None	Adenocarcinoma of rectum

in contrast to the early statistical reviews which reported an incidence of more than 50 per cent.

In Case 36 the patient had three primary neoplasms. The first was an adenocarcinoma of the jejunum, followed 8 years later by a carcinoma of the kidney and a squamous cell carcinoma of the larynx. This patient is also reported to have a carcinoma of the bladder and a carcinoma of the prostate, but histopathologic evidence had not been obtained at this writing.

The time interval between lesions in this group, for the most part, was relatively short.

DISCUSSION

The contributions of clinical medicine to this subject have been limited for several reasons. Foremost is the failure of the medical profession as a whole to report all significant clinical observations and statistical data. Conclusions regarding the incidence of cancer must be based on the relatively small percentage of cases that are reported in the scientific literature and the vital statistics surveys of the few countries publishing reliable reports. The number of cases of primary and multiple malignant disease that remain undiagnosed and unreported is highly speculative. Probably a large majority of these cases are never seen by the medical profession, particularly those in the less civilized parts of the world. Many others no doubt die of accident or intercurrent disease before the second primary malignant tumor manifests itself clinically. Still other cases are undiagnosed at autopsy because of the impracticability of serially sectioning all tissues.

Other limitations to the accuracy of statistics include the diversity of opinion re-

garding the classification of malignant tumors in general and the absence of a set of criteria that will differentiate true multiple primary neoplastic disease from extension or metastasis beyond any question of doubt. Until such criteria have been proposed, tumors having similar histopathologic patterns or occurring in the same system or paired organs will always be subjects of controversy.

The incidence of multiple primary malignant neoplastic disease based on the law of chance has been variously estimated in the neighborhood of 3 per cent. The consensus of opinion seems to favor the theory that the actual incidence is greater than can be accounted for on the basis of chance alone. If this is correct, it seems reasonable to assume that this condition is either an inevitable sequence in the course of uninterrupted neoplastic genesis or that susceptibility, resistance, and heredity factors exist.

The apparent and actual incidence of multiple primary malignant tumors should gradually rise further above the incidence expected on the basis of chance alone because of the following reasons:

1. Progressive improvement in methods for accumulating accurate cancer statistics from all sources should bring more cases to light.

2. Progressive education of the laity, as well as the medical profession, should increase vigilance for the disease and result in earlier diagnosis and treatment.

3. Progressive increase in the number of individuals living in the "cancer age" group should result in an increase in the incidence of multiple primary cancer as well as of initial cases.

4. Progressive increase in the cure and survival rates resulting from improved methods of cancer detection and cancer therapy should permit the occurrence of additional primary tumors in the same individual.

As the actual incidence of cases increases, the clinical significance of multiple primary neoplasms becomes increasingly important from several standpoints. First, the importance of a thorough periodic examination of all cancer patients for the development of subsequent primary lesions as well as metastasis cannot be overemphasized. Secondly, in view of our present knowledge of multiple primary neoplasms and the frequent involvement of the ovaries by a second primary or metastatic lesion following carcinoma of the uterus or gastrointestinal tract, the surgeon must always consider the advisability of castration at the time of surgery for the initial cancer. Furthermore, the problem of castration of premenopausal women with primary carcinoma of the breast, as a method of controlling the development of subsequent primary lesions as well as metastatic lesions, is worthy of consideration.

TABLE VIII.—MULTIPLE NEOPLASMS OF MISCELLANEOUS SYSTEMS

Case No.	Age years	Sex	Diagnosis	Interval	Diagnosis
28	56	M	Squamous carcinoma of the tongue	None	Lymphosarcoma
29	60	F	Sarcoma of nasal septum	1 yr.	Adenocarcinoma of descending colon
30	65	F	Epithelioma of cheek	None	Epithelioma of scalp
31	74	F	Adenocarcinoma of sigmoid colon	None	Myelogenous leucemia
32	65	M	Adenocarcinoma of jejunum	8 yr. 6 mo.	Myelogenous leucemia
33	55	F	Endothelioma of palate	None	Adenocarcinoma of thyroid
34	40	F	Sarcoma of nose	None	Scirrhous carcinoma of breast
35	47	F	Squamous carcinoma of scalp	None	Adenocarcinoma of uterine fundus
36	57	M	Adenocarcinoma of jejunum	8 yr.	Carcinoma of larynx

SUMMARY

A survey of 36 cases of multiple primary malignant neoplasms, based on records obtained from the Department of Surgery at Harper Hospital, revealed an average age incidence of 52.0 years for the appearance of the initial primary tumor, and an average time interval between primary tumors of 3.22 years. There were 32 females and 4 males in this series, a ratio of 8 to 1.

Calculation of the incidence rate in systems and organs reveals that 17 patients, or 47 per cent, had a primary lesion in the gastrointestinal tract; 15 patients, or 41 per cent, had involvement of a breast; and 9 patients, or 25 per cent, had a primary lesion in one ovary.

The time interval between lesions was greatest in those confined to the gastrointestinal system, and shortest in those involving the ovaries and gastrointestinal system.

In this series, there was a family history of cancer in 26 per cent of the cases in which reliable histories were available.

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EDITORIAL

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FRACTURES ABOUT THE ELBOW IN CHILDREN

FRACTURES involving or adjacent to the elbow joint are important, they occur frequently, and excellent functional results are often difficult to obtain. Accurate reduction is required to restore: the carrying angle, flexion, extension, pronation, and supination.

Supracondylar fractures are the most common about the elbow. Volkmann's contracture follows supracondylar fracture more often than any other injury. The anatomy about the elbow joint contributes to impairment in circulation. The distal fragment is usually displaced posteriorly, stretching the terminal portion of the brachial artery over the proximal fragment. At the elbow the brachial artery passes through a closed space bounded posteriorly by the humerus, and laterally and medially by the intermuscular septa which are continuous with the deep fascia that forms the anterior boundary. The occurrence of edema in this space may impair the circulation.

Considering these anatomical facts, circulatory impairment following supracondylar fracture is relatively rare. When it does occur, every effort must be made to restore adequate circulation by correction of the gross displacement of the fracture, elevation, parasympathetic block and, in rare cases, surgery. There are few more distressing conditions seen in the practice of orthopedic surgery than a severe Volkmann's ischemic paralysis.

Nerve lesions are rare, when they do occur the radial nerve is the most often involved, the median second, the ulnar almost never. The radial nerve is subject to injury as it passes over the anterior margin of the proximal fragment in the interval between the brachialis and brachoradialis muscles. Usually the radial nerve paralysis is temporary.

The roentgenograms should be studied to differentiate between supracondylar fracture, condylar fracture, and posterior dislocation of the elbow.

Reduction should be accomplished as soon as possible. General anesthesia is used. Traction is placed on the forearm with the elbow extended and any medial or lateral displacement of the distal fragment corrected by manipulation. While moderate traction is continued, the distal fragment is pushed forward, the proximal fragment backward, and the elbow flexed so that the palm of the hand points toward the sternoclavicular joint. This position places the forearm medial to the arm when the elbow is flexed, therefore, when the elbow is extended the carrying angle will be preserved. The forearm should not be flexed above 45 degrees. If the radial pulse is not palpable at this point, the elbow should be extended sufficiently to allow palpation of the

pulse. The forearm is held in this position by adhesive strapping. When this method is used the circulation must be watched with great care following the manipulation. At the end of 3 or 4 weeks sufficient callus is usually present to allow removal of the adhesive. The child is encouraged to increase the motion in the elbow by active use. Passive motion should not be used. Forceful manipulation or passive stretching of the elbow to produce extension, either by physiotherapist or the relatives is to be condemned as is also the carrying of bricks, books, etc. Active use of the elbow and active use alone should be employed to increase the motion in the joint.

Condylar fractures. It is important to differentiate between supracondylar and condylar fractures. The former can be treated by conservative means in nearly all instances while the latter require early open reduction and adequate internal fixation to insure satisfactory reduction and to prevent disturbances in growth and arthritic changes. Due to the presence of the carrying angle, fractures of the lateral condyle are much more common than fractures of the medial condyle. Fracture or epiphyseal separation of the medial epicondyle is more common than fracture of the medial condyle but not as common as fracture of the lateral condyle.

In either fracture of the medial or lateral condyle, separation and rotation of the fragment is usually seen. The lateral condyle is displaced and rotated by the pull of the extensor muscles, the medial by the flexor muscles. In the roentgenograms the fragments always appear smaller than they actually are as complete ossification of the condyle has not occurred. The condylar fragment is small and difficult to manipulate, as it is practically impossible to grasp and replace it accurately. Even if one is successful in securing an accurate reduction, the pull of the muscles will distract the fragment despite any form of external fixation.

When these fractures are treated by manipulation nonunion occurs. As the fracture line passes through the growth centers of the lower end of the humerus, disturbance in growth will occur. If the lateral condyle is fractured, as the child grows the medial side of the humerus will grow faster than the lateral, thus creating a gradually increasing cubitus valgus deformity. If the medial condyle is fractured the lateral portion of the lower end of the humerus will grow faster than the medial side and there will be gradual decrease of the carrying angle with the development of a gunstock deformity. Irregularity of the lower end of the humerus causes a posttraumatic arthrosis of the elbow. With nonunion of the lateral condyle and increase in the carrying angle, delayed ulnar palsy may be seen during adult life.

To prevent these complications, early operation and internal fixation should be employed. The condylar fragment should be rotated into its anatomic position. In many instances the major portion of the fracture line is covered with cartilage and only a small central area of bone is noted in both fragments. Cartilage heals poorly; consequently, to obtain union it is necessary to oppose the osseous tissue. Internal fixation is imperative to maintain the position of the fragments; without it separation will occur as a result of the muscle pull. The fragment can best be held by means of a small rustless steel nail. If there is a tendency for the condyle to rotate, a second nail may be necessary. The end of the nail should be palpable beneath the skin. At the end of 6 weeks, usually under local anesthesia, the nail is removed.

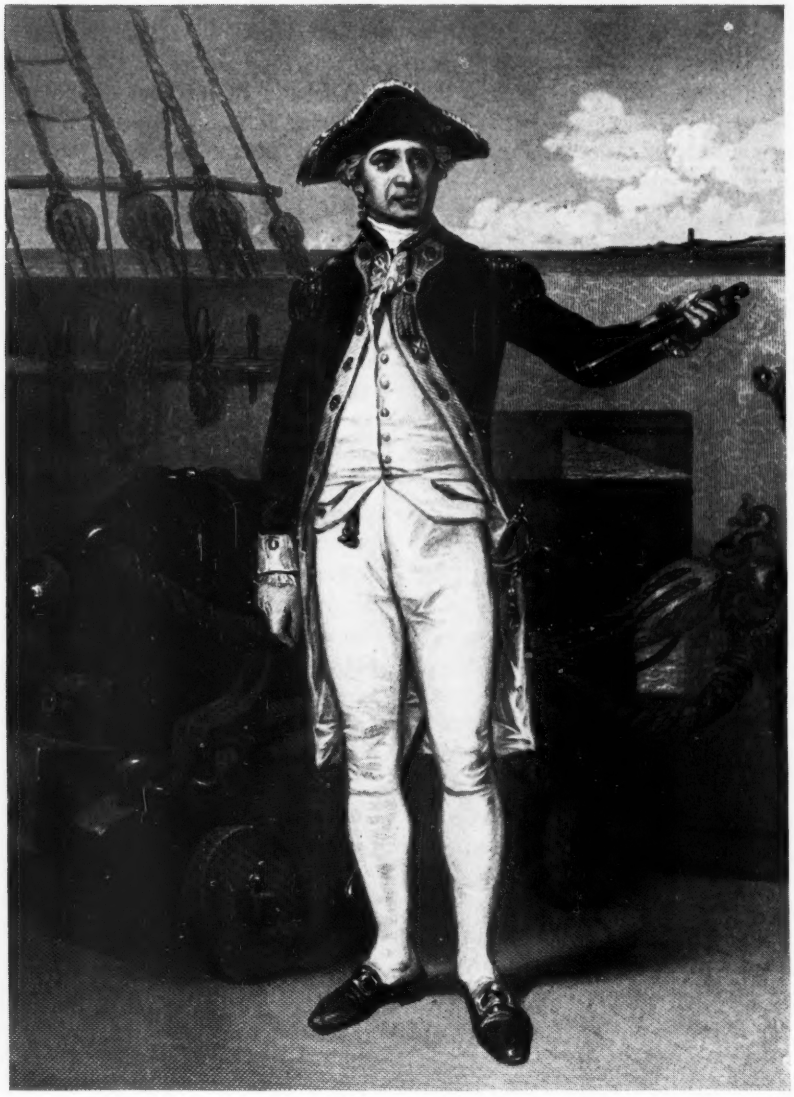
This method has the theoretical disadvantage of passing a foreign body across the epiphyseal line. We have not noted blocking of

the epiphysis or impairment of growth as a result of the nail.

Posterior dislocation of the elbow in children is often associated with fracture or epiphyseal separation of the medial epicondyle. At the time when the dislocation is reduced the medial epicondyle may be caught in the joint.

The above accounts for 90 per cent of the fractures about the elbow in children (supracondylar 65 per cent, condylar 25 per cent, in our series). Fracture of the neck of the radius, fracture of the ulna with dislocation of the head of the radius, fracture of the olecranon and T condylar fractures accounted for the remaining 10 per cent. These are usually treated by methods similar to those employed in adults, except that in fracture of the neck or head of the radius, the head of the radius should not be removed in a growing child as cubitus valgus will result. Also fractures of the ulna with dislocation of the head of the radius can often be treated conservatively in a child while these fractures usually require operative therapy in an adult.

HAROLD B. BOYD.



JOHN PAUL JONES
1747–1792

Death Comes for the Admiral.—Esther H. Vincent.

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DEATH COMES FOR THE ADMIRAL

ESTHER H. VINCENT, Evanston, Illinois

JOHN PAUL JONES started life in a wee cottage in Galloway, in that same western Scotland that nourished Wallace and Bruce, Bonnie Prince Charlie, and Bobbie Burns. His parents, John Paul and Jean Macduff, Low and High Scotch, respectively, handed down to their little son the poetic romanticism of the Lowlanders and the physical vigor and "derring do" of the Highlanders. John Paul, Senior, had come from Fife, where his father was a gardener-innkeeper, and had taken service as a landscape architect on the estate of William Craik, Laird of Kirkcudbright. Craik was the natural son of the eminent surgeon, James Craik, and had achieved a favorable reputation throughout Britain as an inventive agriculturalist.

In their cottage on a granite headland of the Solway Firth, John and Jean Paul produced seven children, four boys and three girls. The two youngest boys, however, died in infancy, and the eldest girl died before she was twenty. The eldest son, William, was adopted by a Virginia planter, William Jones, who took a liking to the lad, while on a visit to his home-folks in Scotland. That left to the family John Paul, Junior, and the two little girls, Mary and Janet.

The future founder of the United States Navy was born on the sixth of July, 1747, the year after the famous battle of Culloden, while the strains of "Scots wha hae with Wallace bled" still echoed over the heather. Efforts have been made to assign him to other than his gardener father—to the Earl of Selkirk on St. Mary's Isle, to Mr. Craik, and to Uncle George Paul. But the probability is that he was quite unromantically legitimate.

His scanty childhood included a meager education at the parish school, and an extensive education at the seashore. His toy frigates had given way to fishing yawls, and his boy companions to bronzed sailors before he was twelve. At that age he was apprenticed to a ship owner, and made his first voyage to the new world. While still in Virginia, he had his indentures returned to him, his ship-owning firm having changed hands, and he went back to Scotland on a British man-of-war. Then as third mate on a "slaver," he plowed the steaming waves to Africa, and at the age of nineteen, found himself chief mate on a Jamaica-Guinea brigantine. In this nefarious trade, sailors died almost as fast as their human cargo, and epidemics were frequent. Young John wrote home about his "several very severe fevers," and at length gave up his job. Stranded in Jamaica, he joined a troupe of actors and toured the West Indies, thus developing his native histrionic ability and achieving skill in speech and stage presence.

Tired of island-jumping, he sailed on a ship bound for Britain. Early in the voyage, both the captain and the first mate died of fever, this sort of thing being quite characteristic of tropical malaria before the days of quinine and of mosquito crusades. John Paul took command, and, on arrival in port, was made master at the age of twenty-one. By this time, his father was dead, and, after arranging family affairs, John again went down to the sea in ships.

Now occurred the unfortunate Mungo Maxwell incident. Maxwell, a fellow Scotsman, was ship's carpenter on a voyage to Tobago. So shiftless and lazy was he, that Captain Paul thought to cure him with the cat-o'-nine-tails. Maxwell seemed none the worse for his whipping, but, when, some time later, he died on another ship, John Paul was accused of his murder. The evidence proved that Maxwell's death was due solely to fever, but the affair put the young captain in a very miserable as well as a precarious situation.

From the Archibald Church Library, Northwestern University Medical School.

His difficulties were not lessened by his own attacks of malarial fever, and by the strain on his constitution occasioned by the summer heat of the tropics. In Tobago, his "isle of misfortune," there later took place another affair of serious import. During a mutiny at sea a rebellious sailor impaled himself on Captain Paul's sword. The twenty-six year old commander was so upset over his two unfortunate experiences with violence, that he disappeared from history for two years. Speculation has suggested that he took refuge in piracy, but there is no worthy evidence as to this, and knowledge of his character contradicts it.

In 1774, John Paul turned up again in Fredericksburg, Virginia, and there found brother William mortally ill. After the funeral, John took over the administration of William's estate, and showed some signs of wanting to become a planter, himself. His glamor-boy personality won for him a rather dazzling social success, and the presence in the neighborhood of a certain Dorothea Dandrige (afterward married to Patrick Henry) was an added incentive to permanent retirement from the sea. But the American Revolution was brewing, and John Paul, who had now added Jones to his name, walked with brisk step from the pillared porches of Virginia to the quarter-deck of a fighting ship.

John Paul Jones was the sort of man who always commands attention. His keen, wild look, heritage of his Highland mother, augmented his charm. Of medium height, he was slender, admirably proportioned, and with classical features. His hair and eyebrows were black, his eyes brilliantly dark. He had a military grace of motion and a remarkable facility of movement. His sweet Scotch baritone fell most agreeably on the ear, and his power of conversation was extraordinary. His dress was invariably good, his personal habits pleasant. His life as a sea captain had produced a certain air of withdrawal, of seeming arrogance, which put lesser men in their places. Since many of these "lesser men" did not like to be put in their places, Paul Jones acquired a good many enemies, some of them in the seats of the mighty.

He reached Philadelphia at the bidding of the Congressional Marine Committee in 1775, and was placed in a group of experienced persons to consider how to make a navy. Now began his life of vexatious delays and bitter disappointments for which all his naval victories and all the adulation of two continents could hardly compensate. Personal jealousies and petty minds continually got in his way. Along with him in the budding United States Navy were "political skippers," soon to be dismissed or to fall into harmless byways. But Jones was the first to hoist the Stars and Stripes as the ensign of the Republic, and was named by Congress to command the *Alfred*, crack frigate of the weak, little American line.

Burgoyne's surrender to Gates at Saratoga was the turning point of the Revolution, and it was Jones who was chosen to carry the news to France in the *Ranger*, the first Yankee frigate to cross the Atlantic. His arrival brought him a new friend in the canny Benjamin Franklin, then Minister to France. It also brought a new friend to the United States, for France now left the harbor of neutrality for the seas of intervention. Jones' association with French admirals, statesmen, nobles and plain citizens added to his own reputation and to that of his country. A series of daring raids on the coast of England, including an incursion to burn the shipping at Whitehaven (across the Solway from his birthplace), gave Britain a frightening experience. In April 1778, the *Ranger* captured the *Drake*, presenting the very new United States with its first victory over a ship of war. But the *Ranger's* commander had the very devil of a time with French and American red-tapism, bungling officials of both nations, treacherous and jealous subordinates, and had the utmost difficulty getting his prize money and meeting his crew pay rolls. All this produced a terrific mental strain on the struggling commander.

But there were interludes of glory and romance in Paris. Flirtatious letters from aristocratic French ladies give proof that one should not write love letters to famous men who keep an orderly correspondence file. Jones received a sword of gold and a medal of merit from Louis XVI, and a purse of 50,000 dollars from his great and good friend, Adelaide de Burbon, Duchess of Chartres. Given command of an old tub of an East Indiaman, *Le Duras*, he changed its name to *Le Bonhomme Richard* in honor of Franklin's "Poor Richard," and set out with three other vessels on the adventure that ended with moonlit victory over the English *Serapis*, and made famous the phrase, "I have not yet begun to fight."

Paris celebrated the conquest with wild delight. The King made Jones a Chevalier, and the Duchess of Chartres greeted him with royal triumph as he laid the English Captain's sword at her feet. News of treachery and conspiracy at home led Jones to return, a "wrathful Achilles of the sea." Congress was suffering from its usu-

al reaction to excessive hero worship, but the riotous passage of the *Alliance* under command of the psychopathic Landais did much to vindicate Jones' honor. Nevertheless, the Scotch-American hero continued to experience disappointment and frustration. Sailing to the Caribbean in vain expectation of a meeting with Spanish and French admirals, Jones had to cope with a long summer of tropical heat and bad food. Already sick with thwarted hopes, he fell easy prey to the marsh fevers of Porto Cabello. Relief came only with autumn and cold water therapy. However, intermittent fever plagued him all his days.

On his return to the States at War's end, he sought recuperation at Pennsylvania's Bethlehem, a favorite health resort for army and navy officers. His name still may be seen in the archives of the hospital kept by the Moravian Brethren. He was only thirty-six years old, but was like a tired and sick old man. Owing to financial reticence on the part of both the United States and France, Paul Jones had to rely on his interest in the whale-oil trade for economic security. But he continued to serve his country generously in spite of inadequate gratitude.

Sent abroad as a special envoy to adjudicate and collect delicate international claims, he proceeded to Paris. Here he had personal interests, also, in connection with the ladies. The most serious love affair of his life was conducted on the fringe of the royal court with a mysterious Mme. T——, said to have been a natural daughter of Louis XV, an apparently very lovable woman, who disappeared in the mists of the Reign of Terror. Jones went on to Copenhagen to play his part in the tragicomedy of the Danish indemnity affair. Landais had holed up American ships in Bergen, then a Danish port, and Denmark had handed them over to Britain. The journey north was accompanied by great physical exposure, and on arrival Jones was forced to spend several days in bed. Hitherto blessed with a Napoleonic imperviousness to small ills, he had finally reached the point where he "couldn't take it."

Paul Jones was now ranking officer in the nonexistent American navy, but, being unemployed for the time, he was open to offers from foreign countries. Catherine of Russia had heard of the handsome naval hero and requested his services. Jones accepted, with French minister Jefferson's blessing, and set out for Unholy Russia. Since direct passage was prevented by ice, Jones made a dangerous detour to Estonia in a small, open boat, manned by a few frightened Swedish sailors. Badly battered, he landed at Revel after several days and nights of constant struggle with cold, wind, waves, and ice. He reached St. Petersburg in April of 1788, and promptly went to bed with a pulmonary upset. This exposure, added to that already suffered on the journey to Denmark, was a deep shock to his already weakened constitution. Exposure to the wiley Catherine and to her treacherous Prince Marshall, Potemkin, was a further shock to the trusting Caledonian.

After a period of flattery and adulation at Court, Jones made the thousand mile journey across the bleak Russian steppes to the pretentious but disease-ridden military post of St. Elizabeth. Both Catherine and Potemkin were potentially dangerous to their new naval advisor, but it was to the interest of both of them that he be given a chance to make use of his talents. His was an uncanny knack of being able to succeed with poor material in both men and ships. And his "I have not yet begun to fight" spirit served him well. Though tired and half-sick, and caught in a net of intrigue, the doughty Russian Vice-Admiral won an astonishing victory over the Turks on the Black Sea. That the inept Prince of Nassau won the glory was characteristic of Russian imperial gratitude.

Three days in an open galley near the Ukrainian port of Kherson was too much for the already feverish naval hero. Hurt and bewildered, he spent two weeks in bed with bronchial pneumonia.

On his return to St. Petersburg, further misery awaited the helpless man in the infamous and senseless Russo-German-girl-scandal, with which courtesan Catherine, in Puritan mockery, tortured her handsome Admiral.

Having wasted his health and his talents in sixteen months of Russian service, Paul Jones asked for and was granted a two year leave of absence. His "retreat from Russia" was made in good order with a "hail the conquering hero" reception in Vienna. May of 1790 found him esconced in a pleasant little house and garden of his own on the Rue de Tournon hard by the Luxembourg. France, already experiencing labor pains preceding the birth of her Revolution, got but little help from the exhausted man. Yellow and emaciated, lonely and sad, the Admiral confined himself to the seasoned joys of a few groups of old admirers. Latterly, he spent his days lying in the garden hammock or sitting in a favorite easy chair in his room. Affectionate respect was his from both the old and the new order in France, and the Revolution touched him but lightly. Social activity became increasingly

difficult for him, owing to frequent and exhausting coughing episodes and to encroaching dropsy. Repeated exposure to cold, stormy weather had affected his respiratory system. The intermittent fevers which had attended him ever since his tropical days had injured his kidneys. The frustrations of a brilliant life had strained his dauntless spirit. Like a ship, sturdy and well built, with strong, beautiful lines, the Admiral was now being broken up prematurely on the rocks of misfortune. Disappointment with light, repeated strokes tortured both body and soul. His spirit had always been strained by a sort of split personality—a clash of the energetic seacaptain (the extravert) with the intensive but unexpressed poet (the introvert).

When Madame Arbergne, his housekeeper, entered his room at about nine o'clock on the evening of July 18, 1792, Death had preceded her. The Admiral lay face downward across the middle of his couch, with his feet on the floor. His arms were outstretched, one hand clutching the counterpane, the other clasping his beautiful watch, gift of the friendly Duchess of Chartres.

Gouverneur Morris, then American ambassador to France, had witnessed his will just three hours before, at the end of a quietly happy afternoon spent with friends in the garden. The attending physician was the great anatomist, Vicq d'Azyr, Marie Antoinette's doctor, and permanent secretary of the Paris Academy of Medicine.

The French Assembly, then sitting, passed a unanimous resolution honoring the memory of Paul Jones, "Admiral of the U.S.A." and decreed that twelve of its members should assist at the funeral. Some even proposed that he be buried in the Panthéon with the illustrious dead of France. But Admiral Jones' body was laid in a cemetery for foreign Protestants, having been put into a leaden coffin, "that, in case the United States . . . should claim his remains, they might be more easily removed." A letter found in the French National Archives of 1792 states that "M. Simoneau has furnished the cost of interment of Admiral Paul Jones, of which the bill amounts to 462 francs."

If he had lived a week longer, Jones would have become an Admiral of France with authority to reorganize the French Navy. Had he lived three weeks longer, he would have received from George Washington orders to take charge of the complicated American interests in European waters, especially those connected with the Barbary pirates.

For one hundred and thirteen years, the body of America's first naval hero lay forgotten in the little cemetery of St. Louis, which became successively a garden, a dumping ground, the site of a laundry, and of several other squalid buildings. Two unsuccessful attempts to locate the grave were made, but it was not until 1905 that Ambassador Horace Porter, by a long and painstaking examination of cemetery records, city maps, and documents, was able to trace the burial place. Five shafts were sunk with galleries in all directions. The intervening spaces were probed by long iron rods. Five leaden coffins were found, of which the third was superior in solidity and workmanship. It contained a well-preserved male body packed in hay, straw, and what had probably been alcohol. Clothed in a winding sheet and linen shirt, the body had its long hair gathered into a monogrammed cap. The flesh was still intact.

Identity was proved by (1) the striking resemblance of the features to the medal made by Dupré, voted by Congress in 1787; (2) anthropologic agreement of measurements with those of the bust of Jones made by Houdon; (3) length of the body, color of the hair, peculiar formation of the ear, and condition of the teeth; (4) the cap marked with the initial "J" made with the loop so rounded as to form a "P" when inverted; (5) the autopsy showing that the subject had had pneumonia and interstitial nephritis.

Dr. Capitan made the autopsy, opening the body from the back in order not to change the appearance of the corpse. He found the viscera much contracted but well preserved. The lungs showed pleural adhesions, especially in the upper lobe. When cut open, they showed a brownish parenchyma. The surface and interior pulmonary tissue presented small white hard masses, three to four millimeters in diameter, somewhat like calcified tubercules. These were particularly prevalent at the level of the diaphragmatic edge of the lower lobe. The heart was grossly normal, but with some flat concretions *sous-endocardiques*, similar to those of the lungs. The liver was a yellow-brown. The healthy gall bladder contained a pale yellow-brown pasty bile. The stomach was very small and contracted. The spleen seemed large in comparison with the other viscera. Both kidneys were small, hard, and contracted. The intestines were contracted and empty. The head was not opened.

Histologic studies revealed a normal heart, with muscle fiber streaks. The seemingly normal liver did not show the cellular lesions expected from the known symptoms of jaundice. The white granulations in the lungs appeared to be tyrosin crystals, products of the decomposition

of azotized substances. No tubercle bacilli could be demonstrated, but there were found small rounded masses, partly calcified, corresponding to patches of bronchopneumonia. The kidney sections showed chronic interstitial nephritis, with thickened vessel walls invaded by sclerosis. Some glomeruli had changed into fibrous tissue in the shape of small spheres.

From the July 19, 1905 edition of the Paris *Le Temps* comes the following:

"We know that the celebrated sailor had manifested some very grave pulmonary symptoms toward the close of his life, and that they were localized in the left lung. Further, that sometime before his death, he had had dropsy of the lower extremities, descending to the feet and ascending to the abdomen, indicating also a renal affection. The autopsy of the cadaver showed the organs impregnated with an alcoholic liquid, contracted, brownish, but so well preserved that Prof. Cornil was able to make histological sections, identical with those of the viscera obtained in an autopsy of our own times. The microscopic examination showed with the greatest exactness, that the liver was normal, that there existed in the left kidney especially, foci of the glomeruli, indicating an advanced interstitial nephritis. These histological lesions accord thus perfectly, we see, with the clinical signs presented toward the end of his life by Jones. It is remarkable that this is the first time that the identification of a cadaver has been realized, by means of these diverse methods, a century after the death of the subject."

The body was brought to Annapolis with due ceremony, and commemorative exercises were held in the Naval Academy's Bancroft Hall on April 24, 1906. There the body rested ignominiously for seven years on a couple of wooden saw horses behind a stairway. On January 26, 1913, one hundred and twenty one years after death, the Admiral's body was finally placed in the crypt of the new Naval Chapel. Cut into the marble of the mausoleum are the names of seven of his ships, including the *Ranger* and the *Bonhomme Richard*.

Napoleon, musing gloomily over Trafalgar, was heard to ask, "How old was Paul Jones when he died?" "Forty-five" was the answer. "He did not fulfill his destiny. Had he lived to this time, France might have had an admiral."

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4. RUSSELL, PHILIPS. John Paul Jones. New York: Brentano's, 1927.
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REVIEWS OF NEW BOOKS

FROM the large volume of material at the Memorial Hospital and the author's wide experience with tumors of bone, Dr. Coley[1] has compiled an informative book which should lead to earlier diagnosis and better treatment. The author stresses primarily the clinical, diagnostic, and therapeutic aspects of the diseases described. The value of the text might have been enhanced by a more complete correlation of the pathologic aspects of bone tumors with their clinical and therapeutic aspects.

The book *Neoplasms of Bone* is organized into sections, and most sections may be profitably read with little reference to the rest of the book. Each section has its own bibliography appended which adds to the completeness of the subject material. Such a division of material into self-contained sections has led to minor overlap of the sections on surgical and constitutional therapy and part of the section on radiation therapy.

The illustrations, including roentgenograms, photographs, photomicrographs, drawings, and statistical tables, in general are numerous and excellent. Illustrative cases are abundantly cited, frequently in detail. The index is large and well chosen.

The author's classification of bone tumors is a modification of the revised classification of the Bone Sarcoma Registry of The American College of Surgeons. Bone tumors are defined as new growths arising in bone or derived from cells which are components of skeletal tissue. They are divided into benign and malignant types and are classified for the most part according to the cell or tissue of which they are composed, as chondroma and chondrosarcoma. However, the term osteogenic sarcoma, instead of being limited to bone-forming sarcoma, is sometimes used later in the text in Ewing's original sense to indicate sarcoma arising in bone, consequently the unsatisfactory terms osteogenic fibrosarcoma and osteolytic osteogenic sarcoma. Again in Chapter 23, the term Ewing's sarcoma is used in the original sense to indicate a specific lesion, endothelioma of bone, and next to osteogenic sarcoma is considered the most common primary tumor of bone. But there is now a large body of evidence that true endothelioma of bone is a comparatively rare lesion and that the great majority of tumors which Ewing described under this head are other types of cancer, as mesenchymal cell sarcoma, reticulum cell sarcoma, neuroblastoma, round cell fibrosarcoma, and other little differentiated sarcomas.

The various theories of cancer etiology are briefly described. The differential diagnosis of bone lesions and a diagnostic survey of such lesions is well done. This includes a discussion of the indications and contraindications of surgical and aspiration biopsy and the technique of each. Relatively few clinics rely upon aspiration biopsy in bone sarcoma to the extent which the author advocates.

There is an excellent chapter by Woodard on blood chemistry in the diagnosis of diseases of bone. It includes a table summarizing the chemical findings in typical cases of bone neoplasms and in non-neoplastic diseases. Especially interesting are the studies correlating alkaline and acid phosphatase levels to primary and metastatic bone tumors.

The benign tumors and tumor-like lesions of bone are covered with considerable detail. However, the discussion of such non-neoplastic lesions as solitary bone cyst, fibrous dysplasia of bone, chondrodystrophia calcificans congenita and so-called non-osteogenic fibroma under benign tumors may serve to link them too closely with the latter. The chapters on chondroma, chondroblastoma, and giant cell tumor are particularly good. The importance of benign tumors, especially chondromatous tumors, as precursors of malignant tumors, is duly considered.

The primary and metastatic tumors of bone are dealt with concisely. The author expresses the desirability of classifying osteogenic sarcoma into 3 groups—osteogenic sarcoma, chondrosarcoma, and fibrosarcoma—to avoid the confusion of further subdivision, but this runs counter to strict classification according to tissue type. A thorough analysis of 283 cases of osteogenic seen and treated at Memorial Hospital is presented. Ewing's tumor, reticulum cell sarcoma, angiosarcoma, and multiple myeloma are similarly analyzed according to clinical features, sex, age incidence, location, treatment, and survival rate. The types and effectiveness of treatment are discussed with each tumor group and again, in more detail, in the special chapters and under surgical and radiation therapy. Of considerable importance is the stress the author gives to the development of osteogenic sarcoma following irradiation. He advises against the use of irradiation therapy for benign lesions for this reason. Amputations are well discussed, including end-results, and treatment of selected cases of bone sarcoma by resection and bone transplantation is properly advocated.

Sections on tumors involving bone by extension, metastatic tumors involving bone (numerically greater than primary bone tumors), tumors of bone in special localities, and lesions of the skeletal system that may simulate neoplasms of bone add to the completeness of the book. Of the latter group the most important under consideration are myositis ossificans, which is all too often confused with osteogenic sarcoma, and Paget's disease in which sarcoma frequently develops.

[1] NEOPLASMS OF BONE AND RELATED CONDITIONS; THEIR ETIOLOGY, PATHOGENESIS, DIAGNOSIS AND TREATMENT. By Bradley L. Coley, M.D. New York: Paul B. Hoeber, Inc., 1949.

This book should be popular with both practitioners and medical students alike.

DALLAS B. PHEMISTER.

THERE is nothing finer in medical literature than the sincere appreciation of the achievements and contributions of those who built the foundations on which modern medical practice is based. When, as has often happened, the builders have had to work alone, and with too little understanding and sympathy from their contemporaries the important part they played may easily be forgotten. For that reason in particular we are under obligation to those who have recorded the story of the pioneers in medicine and surgery and made us aware of our indebtedness to men whose teachings and ideas we constantly apply, perhaps with little thought of their source or little appreciation of our obligation.

In a small and exceedingly interesting volume of 250 pages H. Winnett Orr[1] has told the story of Hugh Owen Thomas, of his nephew, Sir Robert Jones, and of the American orthopedic surgeon, John Ridlon, who made American surgeons aware of Thomas and of his fundamental contributions to surgery. A very thoughtful and scholarly chapter by Arthur Steindler on Ridlon and his share in molding orthopedic surgery and an extensive bibliography add to the completeness and to the value of Dr. Orr's contribution.

Two factors in Thomas' contribution to surgical practice stand out with particular clarity: his constant and persistent emphasis on rest, "enforced uninterrupted and prolonged," and the skill with which he devised methods of providing that rest. That Thomas was a general practitioner and that his application of surgical principles was carried into every phase of his practice is often forgotten by those who think of him only as the originator of the Thomas splint. Orr recalls that Sir Arthur Keith in his interesting essay on Thomas stressed his application of the principle of rest in the treatment of intestinal obstruction rather than in the field with which we invariably associate his name. That important principle of complete rest in the treatment of fractured bones and joint disease is concisely expressed in two quotations from Thomas' small volume, *Diseases of the Hip, Knee, and Ankle Joints*, quoted in Dr. Orr's preface (p. ix).

"I assert that a fractured thigh, if treated by extension only, would be accompanied by vastly more muscular irritability than if the same case was placed in a modern appliance with retention, in which the limb was retained and fixed immovably."

"Efficient and enforced rest in joint disease as well as in fractures, is the infallible remedy for quieting the irritated muscles, not extension."

[1]ON THE CONTRIBUTIONS OF HUGH OWEN THOMAS OF LIVERPOOL, SIR ROBERT JONES OF LIVERPOOL AND LONDON, JOHN RIDLON, M.D., OF NEW YORK AND CHICAGO TO MODERN ORTHOPEDIC SURGERY. By H. Winnett Orr, M.D., with a supplement on Ridlon and his share in moulding orthopedic surgery by Arthur Steindler, M.D. Springfield, Ill.: Charles C Thomas, 1949.

It is interesting to quote beside Thomas' words the author's own comments, on page 25.

"We do not seem to have arrived at this 'rest' point of view for the acutely inflamed fractures and compound fracture wounds. There is still the attempt to diminish the amount of apparatus, to provide more joints and mobility, to make our patients ambulatory, and to render less efficient rather than more so the kind of control which Thomas described long ago as rest, 'enforced, uninterrupted and prolonged.'"

It is this basic principle and the most effective method of securing it to which Orr constantly returns in this study of the three men.

The "Surgery" of Hugh Owen Thomas at 11 Nelson Street in Liverpool in which his nephew, Sir Robert Jones, was associated and in which Jones and his pupils continued their work in later years has often been referred to. Close to the consulting rooms was the brace shop with its smithy, its saddler, and skilled workers. Here it was that Thomas and his aids fashioned the splints and braces that enabled him to provide for his patients the rest upon which he was so insistent. So complete was the equipment and so skillfully designed the splints which he devised, that in Sir Frederick Watson's words, "No matter from what distance a patient comes, no matter whether the affection be spinal caries, hip disease, or fractured thigh, he is always able to return home in an hour or so, most accurately fitted with a simple and appropriate splint."

The work of Jones and of Ridlon is better known to the present generation of American surgeons than that of Thomas. Jones "made acceptable to the profession" the principles which Thomas insisted upon so uncompromisingly. His tact, his diplomacy, and his genius for friendship enabled him to reach a wide and influential audience and to place the specialty of orthopedic surgery in Great Britain upon a firm foundation. Ridlon also, was a powerful influence in American orthopedic surgery during the 40 years that followed the formation of the American Orthopedic Association in 1887. As Dr. Steindler says:

"John Ridlon may be said to represent the connecting link between the American tradition and the rising British influence of such masters as Hugh Owen Thomas and Sir Robert Jones. . . . When he died in 1936 at the age of 84 he left an inspiring memory to his pupils. So sound had been his teachings, so careful, so deliberate, so conservative, and so thoughtful had been his approach to the difficult subjects or problems of our profession, that I do not think anyone of us really believes his methods antiquated nor would any of us hesitate to take counsel with him in any situation if he were alive today."

Everyone interested in orthopedic surgery can gain helpful stimulus and direction by reviewing anew under Dr. Orr's guidance the contributions of these three distinguished surgeons to the treatment of injuries and diseases of bones and joints.

SUMNER L. KOCH.

THE elaborate two volume contribution *Lehrbuch der Geburtshilfe*[1] is written by one of the leading German obstetricians and gynecologists. In the first volume the author discusses the physiology of pregnancy, labor, the puerperium, and lactation, and he discusses multiple births, the healthy newborn infant, and prenatal care. In the second volume he takes up the pathology of pregnancy, dystocia in labor, the pathology of the puerperium, and disturbances of the newborn.

Very little literature is quoted either in the text or at the end of any chapter. This was done intentionally because Martius maintains that physicians who are interested in the literature should consult the large systems of obstetrics. There are 539 illustrations in the first volume and 486 illustrations in the second volume, a total of 1,025 illustrations. Nearly all are highly instructive and many are in color. However, most of the reproductions of x-ray pictures are so poor that they are almost useless.

Throughout both volumes, the author reveals his extensive experience as an obstetrician and as a teacher. His attitude is conservative and in line with that of most obstetricians throughout the world. One minor criticism is that the description and illustration of the Credé maneuver for delivery of the placenta should have been omitted, because this procedure can do great harm. Martius himself emphasizes that this maneuver is "not entirely without danger." Another point of disagreement is the use of oxytocic drugs in cases of placenta previa treated conservatively. Even in a multipara with a marginal placenta previa the use of oxytocics may result in rupture of the lower uterine segment. Aside from these and other minor criticisms the book can be highly recommended to physicians who read German. Martius was assisted by Drs. W. Bickenbach and K. Nordmeyer, and all three deserve great credit for having written these books. The publishers also are to be commended because the paper is good, the type is very clear and all the illustrations except those of the roentgenograms have been reproduced admirably.

J. P. GREENHILL.

THE book *Die geburtshilflichen Operationen; Ihre Ausfuhrung und Anwendung*[2] is the sixth edition to appear since 1934. In it the author discusses the structure of the birth canal and the baby, the mechanism of labor, forceps delivery, breech delivery, version and extraction, embryotomy, repair of lacerations, episiotomy, cervical incisions, pubiotomy, hydrostatic bags, abdominal cesarean section, delivery of twins, treatment of prolapse of the cord and arms, treatment of placenta previa, manual removal of the placenta, uterine tamponade, treatment of abortion, curettement, induction of labor, and sterilization.

There are several minor points with which the reviewer disagrees. The metal hook for the delivery of a breech in a living baby should not be described or illustrated. Likewise the Credé maneuver for expelling the placenta should be condemned and the uterine pack should be given up for controlling bleeding from an atonic uterus. Twenty of the 287 pages and 27 of the 281 illustrations are devoted to destructive operations on the child. This is a disproportionate amount of space and number of illustrations for operations which are now fortunately seldom performed. The only form of tubal sterilization described is the Madlener, though it is our belief that the Pomeroy procedure yields better results.

Aside from these few minor criticisms Martius has written an excellent book which will prove helpful to anyone who reads German. The fact that this is the sixth edition is ample proof that the book has been of great assistance to German students and physicians. The publishers have prepared this book exceedingly well as they have Martius' companion two volume book, *Lehrbuch der Geburtshilfe*.

J. P. GREENHILL.

THE authors present in the monograph *Cardiac Catheterization in Congenital Heart Disease*[3] a brief statement of the methods employed and the information to be gained by cardiac catheterization in infants and children.

The first part of the book outlines the technique employed for the physiologic studies, shows x-ray observations during catheterization, blood pressure tracings within the heart and great vessels, and the formulas for calculation of systemic and pulmonary blood flow and of blood shunts.

The second part of the book reports 27 illustrative cases in which clinical data and catheterization have been co-ordinated in the diagnosis of various types of congenital cardiac malformations.

It is an excellent book which will be read with interest and profit by those who wish to familiarize themselves with this highly specialized diagnostic procedure.

STANLEY GIBSON.

THE second edition of *Operating Room Technique*[4] by Edythe Louise Alexander is a comprehensive presentation of the problems involved in carrying on the surgical work of the hospital.

The material is carefully organized and presented in detail. It is generously illustrated and includes a description of the anatomy involved, operative areas, surgical preparation of the skin, incisions, positions, and sterilization of material to be used in operative procedures.

[1] LEHRBUCH DER GEBURTSHILFE. By Prof. Dr. Med. Henrich Martius. Assisted by Prof. Dr. Med. Werner Bickenbach, Prof. Dr. Med. Kurt Nordmeyer, and Kathe Droysen. Vol. 1: Physiologie; Vol. 2: Pathologie. Stuttgart: Georg Thieme, 1948.

[2] DIE GEBURTSHILFLICHEN OPERATIONEN; IHRE AUSFUHRUNG UND ANWENDUNG. EIN LEHRBUCH FUER STUDIERENDE UND GEBRAUCHSBUCH FUER AERZTE. By Prof. Dr. Med. Heinrich Martius. 6th ed. Stuttgart: Georg Thieme Verlag, 1948.

[3] CARDIAC CATHETERIZATION IN CONGENITAL HEART DISEASE; A CLINICAL AND PHYSIOLOGICAL STUDY IN INFANTS AND CHILDREN. By Andre Cournand, M.D., Janet S. Baldwin, M.D., and Aaron Himmelstein, M.D. New York: The Commonwealth Fund, 1949.

[4] OPERATING ROOM TECHNIQUE. By Edythe Louise Alexander R.N. 2d ed. St. Louis: The C. V. Mosby Co., 1949.

A chapter on the history of asepsis adds much to the interest of this subject.

The author constantly emphasizes the fact that the welfare of the patient is the first consideration, and stresses the necessity of careful planning, cooperation, and teamwork. This volume can be profitably used as a guide and reference for operating room personnel. HAZEL M. JOHNSON.

THE author of *Plaster of Paris Technic*[1] discusses the various forms of plaster used in surgery, giving in detail instructions for handmade plaster bandages. He includes the principles used in the care of the plaster and the application of the various types of plaster casts and a discussion of the errors and difficulties in plaster technique.

A chapter is devoted to the technique of pattern plaster and is well illustrated. The spine, the upper and the lower extremities are dealt with separately in sections. Several chapters are devoted to the use of plaster of paris in war surgery and one chapter is devoted to follow-up care. Approximately one-third of the book is text, the remainder consists of illustrations which are grouped at the end of each chapter.

There has long been a need for a satisfactory text on plaster of paris technique. This book, however, only partially answers the purpose. The brevity of the text combined with the lack of correlation with the illustrations greatly reduces the effectiveness of the book. ERWIN J. CUMMINS, JR.

THE standard *Textbook of Bacteriology*, first written by Hiss and Zinsser in 1910, has been repeatedly brought up to date through 8 editions, first by Zinsser and then by Bayne-Jones. The present group of authors, in preparing the ninth edition,[2] have tried "to keep inviolate the basic biologic approach to bacteriology and at the same time to emphasize the public health significance and the practical clinical importance of certain of the biological characteristics of the organisms."

In preparing this review for SURGERY, GYNECOLOGY AND OBSTETRICS the writer has had in mind the value which this book might have for the surgeon, the gynecologist, and the obstetrician. Certainly the widening of the scope in these three fields of medicine has depended largely on the development and growth of the science of bacteriology. Zinsser himself believed in the close association of his laboratory with the clinical departments, and the present authors, as noted above, clearly expressed their intention of stressing the "practical clinical importance" of the knowledge of bacteria to all departments concerned with infection.

The book is divided into 77 chapters covering a historical review and sections on general bacteriology and immunology. Then the various pathogenic groups are described with special emphasis on the spirochete, the pleuropneumonia group, the rickettsiae, the viruses, and the mycoses. In these chapters reference is made to the clinical manifestations of these organisms. However, the surgeon, gynecologist, and obstetrician would like to see more detailed discussion of the relationship of bacteriology to the operating and delivery rooms, the minutiae of the processes of sterilization and sterile technique, the methods of minimizing the contamination of the "sterile field," and a consideration of carriers of bacteria among operating and delivery personnel. They would also like to see a discussion of the clinical activity of the streptococcus, staphylococcus, pneumococcus, gonococcus, the tubercle bacillus, the aerobic gram-negative rods, the gas gangrene clostridia and the other anaerobic organisms in their clinical fields of interest. These are only lightly touched upon. Furthermore, hardly any reference is made to the work which has been accomplished before, during, and after World War II in the many laboratories of surgical bacteriology. It is hoped that in future editions these practical points will be more fully covered. FRANK LAMONT MELENEY.

THE fourth edition of *Fractures and Dislocations*[3] is divided into two sections. The first section deals with fractures, 7 chapters being devoted to general consideration and principles of care. Fractures of the various bones or groups of bones are dealt with individually in the remaining chapters of the first section.

Part 2 deals with dislocations and is similarly organized. The author recognizes the usefulness of more than one method for the treatment of certain fractures but continues to recommend the one method which he considers the simplest and most reliable for the best functional results. The text material is well organized and well written. Illustrations are excellent, conveniently placed, and referred to frequently in the text. The new developments in traumatic surgery which occurred since the third edition are included in the appropriate chapters. The book effectively fulfills its purpose for the general practitioner. ERWIN J. CUMMINS, JR.

THE technique of retropubic prostatectomy is presented in a monograph of 95 pages entitled *L'Adenomectomie prostatique retro-pubienne*[4] by R. Couvelaire. Many of the problems which are encountered in the performance of this operation are considered, and effective technical methods for their solution are presented. Although the author's technique differs in many minor respects from the excellent method of Terence Millin, the originator of the operation in its present form, the book is well written and concise.

[1] PLASTER OF PARIS TECHNIC. By E. O. Geckeler, M.D. F.A.C.S., 2d ed. Baltimore: The Williams & Wilkins Co., 1948.

[2] ZINSSER'S TEXTBOOK OF BACTERIOLOGY. Revised by David T. Smith, M.D., Donald S. Martin, M.D., M.P.H., Norman F. Conant, Ph.D., Joseph W. Beard, M.D., Grant Taylor, M.D., Henry I. Kohn, Ph.D., M.D., and Mary A. Poston, M.A. 9th ed. New York: Appleton-Century-Crofts, Inc., 1948.

[3] FRACTURES AND DISLOCATIONS; FOR PRACTITIONERS. By Edwin O. Geckeler, M.D., F.A.C.S. 4th ed. Baltimore: The Williams & Wilkins Co., 1948.

[4] L'ADENOMECTOMIE PROSTATIQUE RETRO-PUBIENNE. By R. Couvelaire. Paris: Editions Bernard Baschet, 1948.

This otherwise excellent volume, which is in the form of an atlas and well printed upon glossy paper of good quality, suffers from the poor quality of its illustrations. The numerous photographs are often out of focus and poorly finished; and they frequently fail to demonstrate significant anatomic landmarks. The drawings are also very sketchy and of inferior quality.

FREDERICK A. LLOYD.

THE textbook of surgery for the eye physician *Surgery of the Eye*[1] by a master eye surgeon is a concise and complete treatment of the subject in 392 pages. The details of each step in the surgical procedures are given and aided by the use of many illustrations and diagrams. The contents include first the general considerations for the eye surgeon, preparation of the patient, and a detailed description of the use of local anesthetics. Postoperative treatment includes the use of typhoid-paratyphoid in large doses to which great credit is given. With the varied antibiotics now available such frequent use of foreign proteins in such large doses should be carefully considered.

The operative procedures carefully described include paracentesis, intracapsular and extracapsular extraction of the lens with the management of complications. All of the standard operations for glaucoma are given with the management of complications. Other chapters include the operations on the retina, sclera, cornea, conjunctiva, lids, and sockets including the plastic procedures. The treatment of intraocular foreign bodies is outlined in detail. Surgery for ptosis is considered according to the shortening or advancement of the levator muscle, utilizing the occipito frontalis or the superior rectus muscles. The surgery on the extraocular muscles gives the technique of Todd, Jameson, and Reese. The surgery on the inferior oblique at its insertion which was described by White and later by Berens is not mentioned nor is the more recent surgery on the superior oblique. The book concludes with the description of operations on the tear apparatus.

It is an excellent book and all eye surgeons would be better for reading it or referring to it before the usual or any unusual procedures that they are called upon to do.

BEULAH CUSHMAN.

WITHOUT a doubt *Cancer Metastases*[2] by Hans Walther is one of the finest books of its kind. The author, a roentgenologist, had often encountered cases in which tumor metastases were demonstrable in the bones, the lungs, and in other areas, while the seat of the primary tumor remained unknown. The desire to show a relationship between the location of the original tumor and the seat of the metastases led to a careful study over a 15 year period of the material of the Pathologic Institute at Zurich.

The author has come to the conclusion, and brings abundant proof of the fact, that the spread of tumor metastases always follows the established vascular and lymphatic pathways, and obeys the laws of circulatory physiology. Retrograde transport by reversal of the lymph flow, spread from organ to organ by way of lymphatic channels, and other bizarre explanations for the apparently paradoxical spread of some metastases are vigorously denied. The concept of micrometastases in the lungs, which subsequently lead to a dissemination through the arterial circulation, is a very interesting one, and not only serves to explain many of the pathways of tumor metastases, but also readily lends itself to microscopic proof. The author has established certain rules for hematogenous metastases and divides them into four main types.

This volume throughout gives evidence of great scholarship and a painstaking evaluation of clinical and pathological material. It is printed upon glossy paper of good quality with clear, easily readable type. The illustrations are beautiful and the photography is excellent. The photomicrographs are especially noteworthy and demonstrate a superb histologic technique. This book is a classic in its field and should serve as a standard reference for the clinician as well as the pathologist.

FREDERICK A. LLOYD.

THE *Handbook of Surgery*[3] written by Mekie and Mackenzie is a fine compendium consisting of 41 chapters in 764 pages covering the field of general surgery. Written by teachers of wide experience who obviously know the requirements and limits of a handbook, it is concise but not at the cost of being inadequate. Designed to be of greater value to the senior undergraduate who is interested in a comprehensive review of the essential and important aspects of surgery it has much to offer to both the surgeon and the general practioner.

The chapters follow the pattern of first, a brief discussion of development, anatomy and physiology, followed by symptoms, pathology, clinical examination, treatment, then complications and their treatment. Some chapters have the valuable addition of a section of interpretations of roentgenographic and other clinical laboratory findings; and of a discussion of common errors of interpretation. While any description or discussion of operative techniques is wisely avoided the common generally accepted surgical procedure is named. The orthopedic division, Chapters 30 through 41, is unusually well presented in a book of this design and scope.

The book is new and up to date, but also follows the time proved fundamental principles of surgery. It is a worth-while addition to the surgery texts.

RUSSELL T. BOTHE.

[1] SURGERY OF THE EYE. By Meyer Wiener, M.D. 2d ed. New York: Grune & Stratton, 1949.

[2] KREBSMETASTASEN. By Dr. Med. Hans E. Walther. Basel: Benno Schwabe & Co., 1948. (Imported by Grune & Stratton, Inc., New York.)

[3] HANDBOOK OF SURGERY. By Eric C. Mekie, M.B., Ch.B., F.R.C.S.(Edin.), F.I.C.S., and Ian Mackenzie, M.B.E., Ch.B., F.R.C.S.(Edin.). Foreword by the late Sir John Fraser, Bart., M.C., M.D., Ch.M., F.R.C.S.(Edin.). 2d ed. Baltimore: The Williams & Wilkins Co., 1949.

THE author, the professor of surgery at the University of Kiel, reviews in the 190 page monograph entitled *Pathologische Physiologie der frischen, geschlossenen Hirnverletzung, insbesondere der Hirnerschuetterung*[1] the literature on closed cerebral injuries and his own experiences with such injuries. He found that the majority of the patients who died of cerebral concussion had severe circulatory and vascular changes in the internal organs and especially the lungs. He describes a "centrogenic" pulmonary hemorrhage which he found to be caused by lesions in the hypothalamic region. Carefully evaluated animal experiments also revealed the same changes. Similar circulatory changes and hemorrhages in the heart, the liver, the kidneys, the pancreas, the spleen, and the lungs could be produced by small puncture lesions in the hypothalamic nuclei, and he concluded that the hypothalamic nuclei were the seat of a sympathetic and parasympathetic center which regulated peripheral circulation. Lesions of this center produced the peripheral circulatory changes which resulted in death.

He studied the various clinical changes which followed closed craniocerebral injuries and correlated them with experimental findings. Blood pressure, blood picture, blood distribution, respiration, body temperature, protein and carbohydrate metabolism, electrolyte and fluid balance, basal metabolic rate showed reversible postconcussion changes which were thought to be the result of stimulation of the sympathetic and parasympathetic center or of its pathways in the brain stem.

Posttraumatic symptoms and findings are also discussed; they include chapters on headaches, vertigo, oculomotor disturbances, temperature and blood pressure changes, and changes in bladder, sexual, vasomotor and metabolic function. Chronic posttraumatic disturbances were present in 30 per cent of the cases. They depended to a large extent on the pretraumatic personality of the patient himself.

Another chapter deals with the morphologic and functional findings of the injured brain and especially the etiology and pathology of cerebral swelling and edema causing posttraumatic increased intracranial pressure. Cerebral contusion, petechial and massive intracerebral hemorrhages are also mentioned. Spinal fluid, encephalographic and ventriculographic findings are discussed and their common relation to the development of cerebral edema arising on the second and third posttraumatic day is demonstrated. Arteriograms showed contraction of the cerebral vessels in concussion while they usually showed widened and poorly filled vessels in cases of contusion.

In his last chapter, the author discusses the prognosis and the treatment of fresh craniocerebral injuries; the indication and effect of dehydration, osmotherapy, spinal or ventricular puncture and surgical intervention are briefly presented. His best results were obtained by bed rest, dehydration and osmotherapy. GEORGE PERRET.

[1] PATHOLOGISCHE PHYSIOLOGIE DER FRISCHEN, GESCHLOSSENEN HIRNVERLETZUNG, INSBESONDERE DER HIRNERSCHUETTERUNG; KLINISCHE, ANATOMISCHE UND EXPERIMENTELLE BEFUNDE. By R. Wanke. Stuttgart: Georg Thieme, 1948.

IN the third edition of a paper bound monograph, *Technique de la chirurgie du sympathique et de ses infiltrations*[2], Doctors O. Lambret, P. Razemon, and P. Decoulx have presented an interesting discussion of techniques for various forms of sympathectomy and for use of novocain block. It should afford valuable reading for those interested in this field of surgery. Not included in the book are several of the newer procedures recently developed and often employed. However, included in it are interesting and apparently accurate drawings of the relationships of the sympathetic nerves and their ganglionated paravertebral chains to surrounding structures. It should prove interesting reading for those familiar with the French language and familiar with standard techniques for sympathectomy and the indications for use of block or excision of the ganglia and sympathetic chains. KEITH S. GRIMSON.

THE text *Pulmonary Tuberculosis*[3] was first presented in 1939. The second edition has been completely revised, enlarged, and modernized. The task of revision has been the lot of W. Pagel since Laurence O'Shaughnessy met death while in military service in 1940, and Gregory Kayne succumbed to illness in 1945. Dr. Pagel has felt the loss of his stimulating partners, but has met the situation with the aid of carefully selected coauthors (F. A. H. Simmonds, N. Macdonald, and L. Fatti). These men, in a splendid co-operative venture, have dedicated their edition to their lamented confreres.

The pathological, clinical, and surgical aspects of pulmonary tuberculosis, including current concepts of antibiotic therapy, are presented. An extensive bibliography and usually a chapter summary is found at the end of each section. This group of Middlesex England physicians has compacted into this 720 page volume most of the essential information regarding pulmonary tuberculosis. The disease is thoroughly though concisely presented; controversial points are discussed with an open mind. Anyone interested in the field of tuberculosis will find this book of value. EUGENE L. WALSH.

GOOD books in English on ocular histology and pathology for reference and study have been sadly lacking in the past. The few that have been available are either out of date or very incomplete. The result is that the subject of ocular pathology has been neglected by a large number of practitioners and students of ophthalmology.

[2] TECHNIQUE DE LA CHIRURGIE DU SYMPATHIQUE ET DE SES INFILTRATIONS. By O. Lambret, P. Razemon and P. Decoulx. 3d rev. ed. Paris: G. Dion & Cie, 1948.

[3] PULMONARY TUBERCULOSIS; PATHOLOGY, DIAGNOSIS, MANAGEMENT AND PREVENTION. By G. G. Kayne, W. Pagel, and L. O'Shaughnessy. 2d ed., rev. and partly rewritten by Walter Pagel, M.D., F. A. H. Simmonds, M.A., M.D., D.P.H., N. Macdonald, M.B., M.R.C.P.(Ed.), and L. Fatti, F.R.C.S. London, New York and Toronto: Geoffrey Cumberlege; Oxford University Press, 1948.

Thanks to Professor Sommers, who is well qualified by many years of experience in working with and teaching the subject of ocular pathology, there is now available a satisfactory treatise on the subject.

His book *Histology and Histopathology of the Eye and its Adnexa*[1] is divided into three parts. Part 1 has to do with normal histology, embryology, and senescence; Part 2 with general pathology (from an ocular viewpoint); and Part 3 with histopathology of the eye. This covers very well the various structures of the eyeball and adnexa. In addition, there are valuable chapters on ocular developmental abnormalities, glaucoma, myopia, injuries, and the pathologic conditions that arise as the result of surgery.

[1]Histology and Histopathology of the Eye and Its Adnexa. By I. G. Sommers, M.D. New York: Grune & Stratton, 1949.

At the end of each chapter, under the heading "Reading of Source Material" there are remarks on the pertinent discussion by many authors, taken from their writings. This is one of the most interesting and valuable parts of the book. It contains a wealth of information and should act as a stimulus for further study by the reader.

The book is well printed and illustrated. Perhaps more illustrations could have been used to advantage, for the subject is complex and difficult and the reading of it makes for tough going at times. The ophthalmologist will be well repaid in the development of his understanding of his clinical problems for the effort that is required in a careful study of Sommer's excellent and exhaustive work.

Derrick Vail.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

Operative Technic in Specialty Surgery. Edited by Warren H. Cole, M.D., F.A.C.S. Introduction by Allen O. Whipple. New York: Appleton-Century Crofts, Inc., 1949.

Diseases of the Aorta; Diagnosis and Treatment. By Nathaniel E. Reich, M.D., F.A.C.P. New York: The Macmillan Co., 1949.

Childbirth; Your Questions Answered. By Carl Henry Davis, M.D., and Donita Ferguson. New York: Harper & Brothers, 1949.

A Manual of Physical Therapy. By Richard Kovács, M.D. 4th rev. ed. Philadelphia: Lea & Febiger, 1949.

Electrotherapy and Light Therapy; with Essentials of Hydrotherapy and Mechanotherapy. By Richard Kovács, M.D. 6th rev. ed. Philadelphia: Lea & Febiger, 1949.

Modern Surgical Technic. By Max Thorek, M.D., LL.D., Sc.D., F.I.C.S., F.B.C.S., D.C.M. With a foreword by Fred W. Rankin, B.A., M.A., M.D., LL.D., Sc.D., F.A.C.S. 2d ed. Vols. 1, 2, 3, 4, and index. Philadelphia, London, Montreal: J. B. Lippincott Co., 1949.

An Introduction to Clinical Surgery; Surgical Wherefores and Therefores. By Charles F. M. Saint, C.B.E., M.D., M.S., F.R.C.S. (Eng.), Hon. F.R.A.C.S., Hon. F.G.S.S. Cape Town and Johannesburg: Published for The Post-Graduate Press by Juta & Co., Ltd., 1949.

Bone and Joint Radiology. By Emerik Markovits, M.D. New York: The Macmillan Co., 1949.

Die Dystrophie. By Professor Dr. Med. Heinrich Berning. Stuttgart: Georg Thieme Verlag, New York: Grune & Stratton, Inc., 1949.

Grundlagen der funktionellen urologischen Roentgendiagnostik. By Dr. Med. Habil. Walter Pfeifer. Stuttgart: Georg Thieme Verlag, New York: Grune & Stratton, Inc., 1949.

Golden Jubilee World Tribute to Dr. Sidney V. Haas. New York: The Committee for the Golden Jubilee Tribute to Sidney V. Haas, 1949.

Annals of Roentgenology; a Series of Monographic Atlases; Roentgen Diagnosis of Diseases of the Skull. Vol. 19. By Max Ritvo, M.D. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1949.

Abraham Levinson Anniversary Volume; Studies in Pediatrics and Medical History. Edited by Dr. Solomon R. Kagan, and Dr. Isaac A. Abt, Dr. Reuben Friedman, and Prof. Max Neuburger. New York: Froben Press, Inc., 1949.

The Thomas Vicary Lecture 1948; The Portraiture of William Harvey. By Geoffrey Keynes, M.A., M.D. (Cantab.), F.R.C.S.(Eng.). London: The Royal College of Surgeons of England, Lincolns Inn Fields, 1949.

Chirurgia d'urgenza. By Stefano Teneff. Torinto: Edizioni Minerva Medica, 1949.

A Short Practice of Surgery. By Hamilton Bailey, and R. J. McNeill Love. Illustrations by L. C. D. Hermitte, 8th ed. Baltimore: The Williams & Wilkins Co., 1949.

Atlas of Surgical Operations. By Elliott C. Cutler, and Robert M. Zollinger. Illustrated by Mildred B. Codding, A.B., M.A. 2d ed. New York: The Macmillan Co., 1949.

Functional Localization in Relation to Frontal Lobotomy. By John F. Fulton, O.B.E., M.D., D.Sc., LL.D.(Birm.) Being The William Withering Memorial Lectures Delivered at The Birmingham Medical School, 1948. New York and London: Oxford University Press, 1949.

A Textbook of Surgery. By American Authors. Edited by Frederick Christopher, B.S., M.D., F.A.C.S. 5th ed. Philadelphia and London: W. B. Saunders Co., 1949.

Cirugia de la glandula tiroides; anatomia quirurgica del cuello el nervio laringeo superior y su relacion con la fisiologia laringea las aponeurosis cervicales. By Diego E. Zavaleta. Buenos Aires: Ediciones Impaglione, 1949.

Minutes of the Seventh Streptomycin Conference. Held on April 21, 22, 23, and 24, 1949, Cosmopolitan Hotel, Denver, Colorado. Prepared and edited by Veterans Administration, Area Office, Washington, D.C.

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*McLester, J. S.: Protein Comes Into Its Own, J.A.M.A. 139:897 (April 2) 1949.

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2. Underwood, O. B.; Gaul, L. E.; Collins, E., and Mosby, M.: J.A.M.A. 130:249, 1946.
3. Andrews, G. C.: Diseases of the Skin, Philadelphia, W. B. Saunders Co., 1945.
4. Gaul, L. E.: J.A.M.A. 127:439, 1945.

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